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TABLE OF CONTENTS FIRST PAGE

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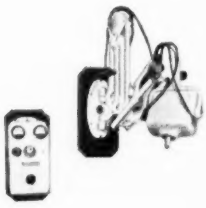

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CONTENTS

Editorials

PAGE

Society Transactions 345

Original Articles

Follicular Lichen Planus (Lichen Planopilaris)
Henry Silver, M.D.; Louis Chargin, M.D., and Perry M. Sachs, M.D., New York 346

Use of a Cycloheximide Medium for Isolation of Dermatophytes from Clinical Materials
Lucille K. Georg, Ph.D., Chamblee, Ga 355

Observations on Anticomplementary Reactions
Andrew George Lighter, M.D., Los Angeles 362

Unusual Forms of Solar Dermatitis
Robert J. Morgan, M.D.; Paul O. Shackelford, M.D., and John H. Lamb, M.D., Oklahoma City 369

Nonpigmented Malignant Melanoma D'Emblée
Hugo Hecht, M.D., Cleveland 380

Dermatitis Venenata Due to Native Woods
Leonard F. Weber, M.D., Chicago 388

Squamous Cell Carcinoma of the Vulva Secondary to Granuloma Inguinale
Lee J. Alexander, M.D., Dallas, Texas, and Thomas L. Shields, M.D., Fort Worth, Texas 395

Mycosis Fungoides
A. Irving Sweiller, M.D.; Frederic Feldman, M.D., and Maurice Morrison, M.D., Brooklyn 403

Lichen Amyloidosus Associated with Varicose Veins
Max Wolf, M.D., New York 407

Clinical Notes, New Instruments and Techniques

Lupus Vulgaris Treated with Isoniazid
Robert E. Holsinger, M.D., Indianapolis 413

Society Transactions

Chicago Dermatological Society 419

New York Academy of Medicine, Section of Dermatology and Syphilis 424

Philadelphia Dermatological Society 431

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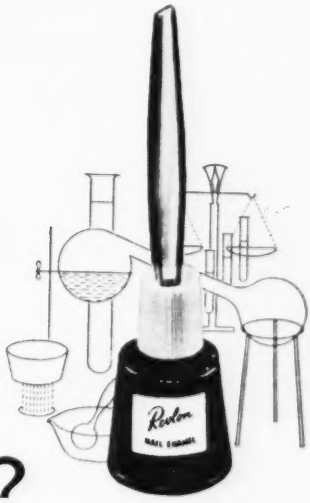

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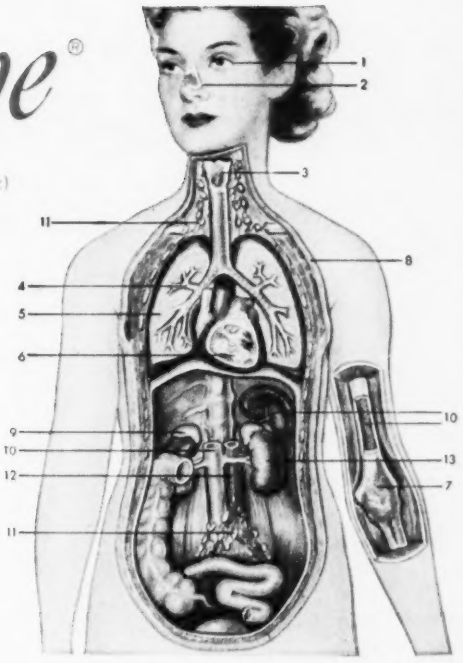

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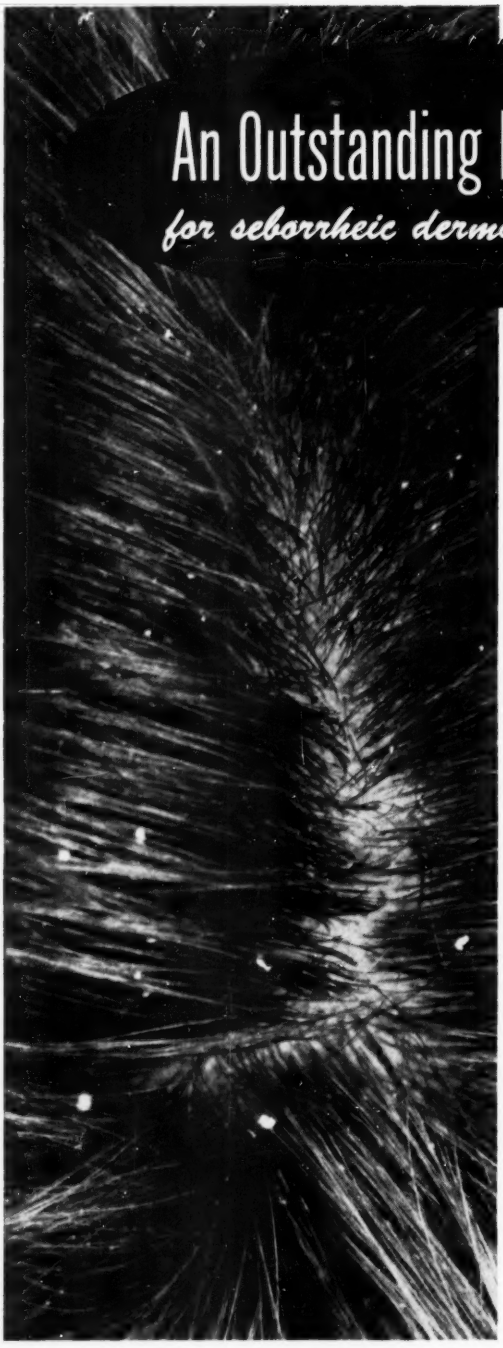

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1. Slinger, W. N., and Hubbard, D. M. (1951), Arch. Dermat. & Syph., 64:41, July.
2. Slepyan, A. H. (1952), *Ibid.*, 65:228, February.
3. Ruch, D. M. (1951), Communication to Abbott Laboratories.

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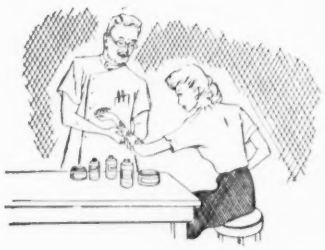

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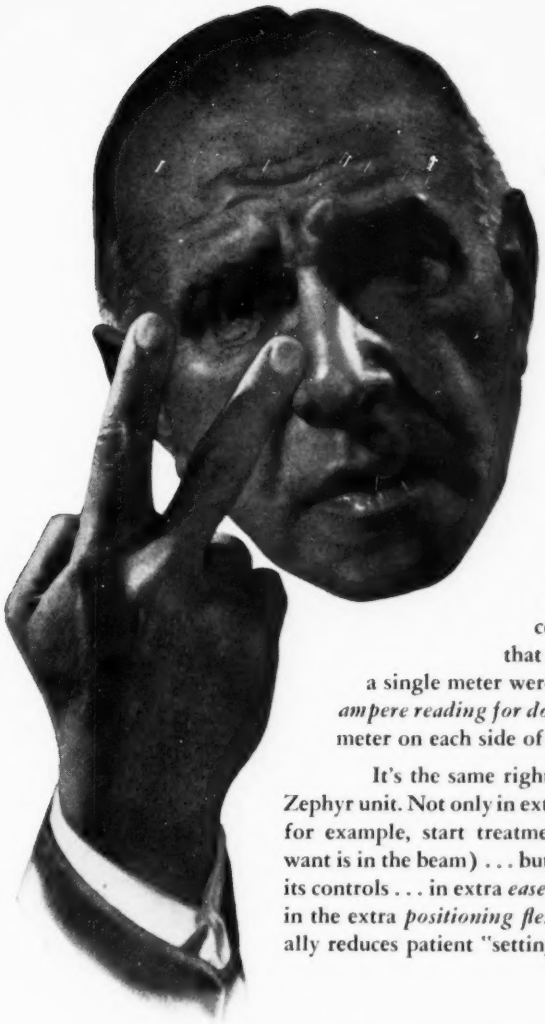

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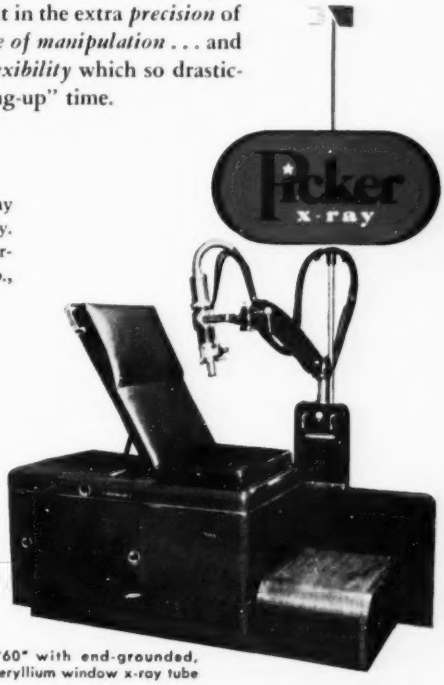

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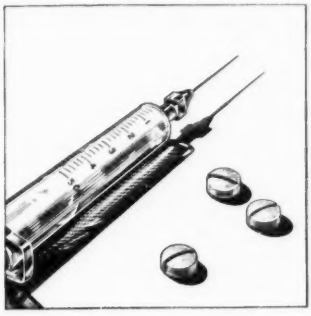

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*Sulzberger, M. B., and Wolf, J.: Dermatology, Essentials of Diagnosis and Treatment, Chicago, Year Book Publishers, Inc., 1952, p. 323.

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A. M. A.
Archives of Dermatology and Syphilology

VOLUME 67 APRIL 1953 NUMBER 4

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Editorials

SOCIETY TRANSACTIONS

The Transactions of the various Dermatologic Societies, as published in the ARCHIVES, have been the cause for some discussion in recent years. The sharp increase in the number of dermatologists and the many new dermatologic societies, with the consequent increase in the amount of discussions, have created many more pages of material than we are able to print, so that a new policy in presenting these reports was necessary. A supplemental issue limited to Transactions was published in November, 1949, and recently it was thought advisable to prepare another one. However, as there were some differences of opinion as to the desirability of this, it was decided to make a spot survey by mail of our subscribers to find out how many were willing to pay an additional assessment of $3, the cost for two such issues.

The results of the survey were surprisingly informative. The replies indicated that only 57% of the subscribers were willing to pay the cost of preparing the two numbers, and 43% were opposed to the idea. Of those who objected, slightly more than half were accredited dermatologists, while general practitioners, hospitals, and other medical libraries made up the remainder.

Therefore, to meet the wishes of the many readers who voted against the supplementary issue, it was decided not to publish a supplement until such time as this will not impose an additional hardship on the subscribers.

FOLLICULAR LICHEN PLANUS (LICHEN PLANOPILARIS)

HENRY SILVER, M.D.
LOUIS CHARGIN, M.D.
AND
PERRY M. SACHS, M.D.
NEW YORK

IN THIS study we have directed our effort toward clarification of a syndrome most appropriately termed follicular lichen planus, which has been the subject of considerable discussion since the turn of the century. The British and American authors who kept the discussion alive have progressively contributed to the better understanding of the disease. In the following brief historical review, we will evaluate the accumulated material which helped crystallize our concept of the disease.

The disorder was labeled lichen planopilaris by Pringle [1] in 1895. At a meeting of the Dermatological Section of the Royal Society of Medicine on April 15, 1915, Little [2] presented a patient showing "cicatricial alopecia" of the scalp, together with a follicular eruption on the body, indistinguishable clinically from lichen spinulosus. The relation of the follicular lesions of the scalp to the follicular lesions of the body was debated, and Little expressed the opinion of the unity of the pathologic process and named it "folliculitis decalvans et atrophicans." In 1919,[3] after study of his second case, he suggested that lichen planus probably could explain all the manifestations of the disease.

In 1926, in an article published in the *Dermatologische Wochenschrift*,[4] Little recorded his observations on six cases, all in women, and stated, "The conclusion is inevitable that this syndrome is a variety of lichen planus hitherto undescribed." He also analyzed Pringle's cases and called attention to the absence of the "remarkable symptom of cicatricial alopecia." He suggested that it is perhaps permissible to think that this feature was overlooked.

Feldman, in 1922 [5] and later in 1936,[6] fully discussed the syndrome on the basis of personal cases and a review of the recorded cases. He took issue with

Read at the Tenth International Congress of Dermatology, London, July 23, 1952.

1. Pringle, J. J., cited by Adamson, H. G.: Folliculitis Decalvans et Atrophicans: Report of a Case, Brit. J. Dermat. **17**:264, 1905.

2. Little, E. G.: Folliculitis Decalvans et Atrophicans: Report of a Case, Brit. J. Dermat. **27**:183, 1915.

3. Little, E. G.: Lichen Spinulosus et Folliculitis Decalvans: Report of a Case, Proc. Roy. Soc. Med. **14**:67, 1921.

4. Little, E. G.: An Undescribed Variety of Lichen Planus, Dermat. Wchnschr. **91**:1203, 1930.

5. Feldman, S.: Lichen Planus et Acuminatus Atrophicans, Arch. Dermat. & Syph. **5**:102, 1922.

6. Feldman, S.: Lichen Planus et Acuminatus Atrophicans: Folliculitis Decalvans et Lichen Spinulosus of Little, Arch. Dermat. & Syph. **34**:378, 1936.

Little's designation of the disease as lichen spinulosus et folliculitis decalvans or folliculitis decalvans et atrophicans and contended that these are misnomers. He maintained that the horny follicular plugs bear a relationship not to lichen spinulosus but to lichen planus, and for want of a better name he labeled the lesions "acuminatus." This served to confuse particularly the European dermatologists, who associated the term with lichen ruber acuminatus. Further confusion resulted from the fact that the second part of Little's designation, "folliculitis decalvans," is also the name of an unrelated disease of the scalp associated with pustules and scarring, i. e., folliculitis decalvans (Quinquaud). Feldman, however, was in accord with Little's correct interpretation of the disease process as belonging to the group of lichen planus. A further contribution was his insistence that this dermatosis is a combination of lichen planus and a follicular type of the same disease. However, he claimed that both forms show atrophy, an interpretation which we believe is not fully correct. His argument that this disease is closely allied to lichen sclerosus et atrophicans of Hallopeau, in the light of our present knowledge, is erroneous. Among others, Montgomery and Hill,[7] especially, have shown that lichen sclerosus is a disease entity and is unrelated to lichen planus.

Before and since the papers of Little and of Feldman, to both of whom belong the credit of identifying the true nature of the disease, many cases have been recorded and studied. Some contain pertinent discussion, but especially commendable are the articles of McCafferty, Ellis and Kirby-Smith, and W. Sachs and DeOreo.

In 1928, McCafferty,[8] under the title "Folliculitis Decalvans and Atrophicans (Little)," fully recorded the clinical and pathological features of a case. He analyzed the previously reported cases and the various views expressed up to that time. He gave due credit to Little for pointing out the identity of the body and scalp lesions, but his personal conclusion was that the process is a variant of ulerythema ophryogenes Unna-Taenzer or of lichen spinulosus.

A careful reading of the clinical description and pathological observations seems to justify the conclusion that his case may in fact have been one of follicular lichen planus in which the planus lesions were at that time absent or not identified.

Ellis and Kirby-Smith[9] followed Feldman's terminology and concept, namely, that the disease is a form of lichen planus associated with acuminate papules. W. Sachs and DeOreo[10] expressed the view that atrophy is present only in a clinical and not in a pathological sense. Their opinions are more thoroughly discussed in the paragraphs on the pathological aspects.

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7. Montgomery, H., and Hill, W. R.: Lichen Sclerosus et Atrophicus, Arch. Dermat. & Syph. **42**:755, 1940.

8. McCafferty, L. M.: Folliculitis Decalvans et Atrophicans (Little), Arch. Dermat. & Syph. **18**:514, 1928.

9. Ellis, F. A., and Kirby-Smith, H.: Lichen Planus et Acuminatus Atrophicans (Feldman): Folliculitis Decalvans et Lichen Spinulosus (Little), Arch Dermat. & Syph. **43**:628, 1941.

10. Sachs, W., and DeOreo, G.: Lichen Planopilaris: Lichen Planus et Acuminatus Atrophicans (Feldman) and Lichen Spinulosus and Folliculitis Decalvans (Little), Arch. Dermat. & Syph. **45**:1081, 1942.

Fig. 1 (Case 1).—Lichen planus and spinous lesions of the wrist and forearms.

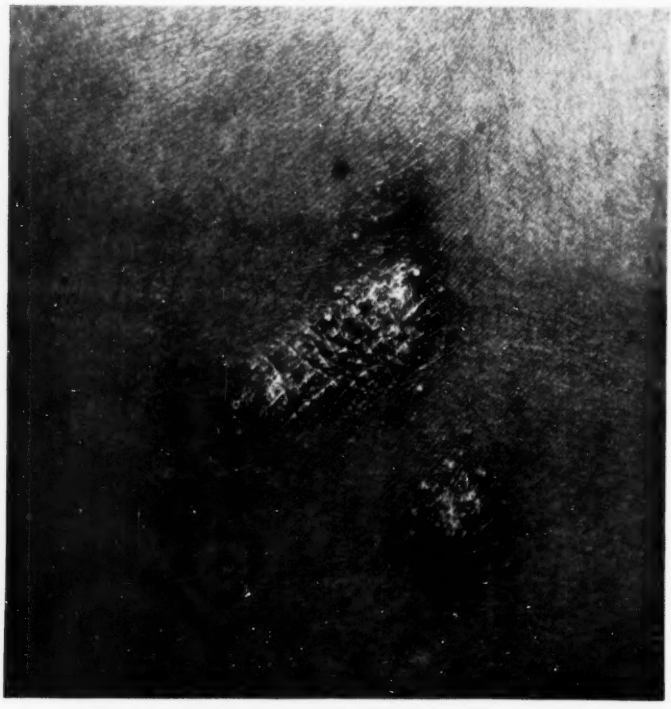

Fig. 2 (Case 1).—Close-up view showing spinous lesions.

REPORT OF CASES

CASE 1.—H. B., a white woman aged 18 years, presented an eruption of three years' duration involving the forearms, wrists, and lower extremities (Fig. 1). The eruption consisted of patches varying from 0.5 to 5 cm. in diameter, showing follicular spinous lesions (Fig. 2) and lichen planus lesions. The scalp and oral mucosa were free of eruption.

The histologic examination of a section taken from the left inner thigh revealed dilated follicles filled with densely laminated horny material (Fig. 3). The walls of these follicles were acanthotic; the granular layer was increased, and the basal cell layer was washed out. Adjacent

Fig. 3 (Case 1).—Features of lichen planus involving the follicles; hematoxylin and eosin stain.

to the follicles was a band-like infiltration of small round and wandering connective tissue cells. Throughout the entire subepidermic region was an intense band-like infiltration of similar cells. In several zones in the subepidermic region were clusters of chromatophores. There was moderate interstitial edema throughout the remaining cutis. The epidermis was irregularly acanthotic, in places flattened, and the palisade layer in many areas was washed out. The granular and horny layers were increased. There were no other important changes. The elastic tissue was present throughout, except in the areas of cellular reaction. These zones showed the elastic tissue to be pushed aside. The histologic diagnosis was lichen planopilaris and lichen planus.

Case 2[11].—L. H., a white housewife aged 47, presented an eruption of six months' duration involving the scalp, back, and extremities. The areas contained numerous scattered discrete papules the size of a pinhead and patches studded with acuminate keratotic papules. The arms showed atrophic and pigmented spots. On the buccal mucosa and tongue there were whitish papules and streaks forming a lace-like pattern, typical of lichen planus. The fingers and toenails presented dystrophic changes. On the scalp was a patch of alopecia with an atropic center and keratotic follicles at the borders. The histologic diagnosis was lichen planopilaris.

Case 3.[12]—C. M., a Puerto Rican woman aged 36, presented an eruption of two years' duration, with onset on the scalp. Inactive pigmented lesions were also present on the forehead, left ear, upper lip and jaw.

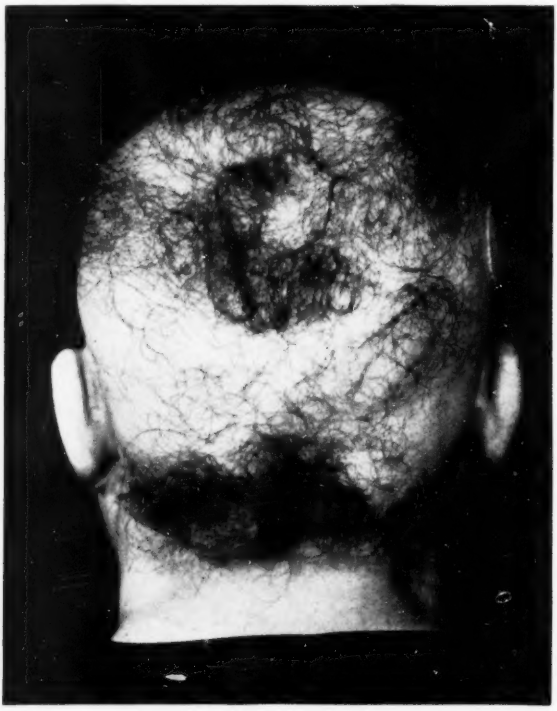

Fig. 4 (Case 3).—Scalp showing spinous lesions, alopecia, and clinical atrophy.

There was a suggestion of atrophy in front of the left ear. On the shoulder the lesions were of lichen planus type (Fig. 4). Anteriorly on the scalp there was an erythematous atrophic area of alopecia in which hyperkeratotic patulous follicles were seen (Fig. 4). The left buccal mucosa showed features of the type seen in lichen planus of the mucosa. Itching was present.

The histologic examination of a section taken from a lesion of the shoulder revealed lichen planus. Examination of a specimen taken from the scalp showed lichen planopilaris.

Case 4.—S. C., a woman aged 42, was first seen in 1946 presenting a disease of the scalp followed by loss of hair. An active folliculitis and areas of atrophy were present. The arm

11. This case was presented at the meeting of the Bronx Dermatological Society, Jan. 17, 1946.

12. This case was from the Department of Dermatology of the New York Medical School, Flower and Fifth Avenue Hospitals (service of Dr. E. F. Traub).

and under surface of the breasts showed a disappearing lichen planus with clinical atrophy. Six years later, in 1951, the body was free of eruption, except for two patches of atrophy. The scalp showed superficial atrophy with scattered tufts of hair. There was no regrowth of hair.

Roentgenograms of the sella turcica and endocrinologic studies showed no abnormalities.

The histologic examination of a section taken from the scalp disclosed a mild focal reaction in the upper cutis. There was evidence of two hair follicles, one of which contained a hair, while fibrosis was seen about the other. The epidermis was thin and showed no changes. The elastic tissue was normal, with a mild decrease around the follicle. The picture was one of loss of the pilosebaceous apparatus compatible with the pathological picture of pseudopelade and may well be interpreted as the terminal stage of lichen planopilaris.

CLINICAL CHARACTERS

Our comments are based on the study of 4 personal cases and on an analysis of 101 cases culled from the literature which presented more or less complete data.

TABLE 1.—*Analysis of 105 Cases*

	%
Sex	
Male	37
Female	63
Alopecia	42
Atrophy of the scalp	40
Lichen planus plus spinous lesions	72
Spinous lesions plus atrophy of the scalp	34
Clinical triad	40
Histologic features recorded	45

TABLE 2.—*Duration of Disease and Age Distribution*

Duration								
Yr.	½	½-1	1-2	2-3	4-5	5-8	8-9	9-10
%	39.7	15.1	20.5	7.8	1.9	7.6	1.9	5.7
Age								
Yr.	1-10	10-20	20-30	30-40	40-50	50-60	60-70	70-80
%	2.3	12.3	7.8	18.8	17.8	18.8	18.8	3.4

There are many other cases recorded which probably belong in this category but include inadequate data for evaluation.

The clinical picture of this disease has been described as a triad consisting of lesions of lichen planus, spinous or acuminate lesions, and alopecia of the scalp or other hairy regions frequently showing clinical atrophy. The spinous lesions are, of course, always present; the others are not. The combination of lichen planus and spinous lesions was present in 72% of the cases, while in 34% spinous lesions were associated with atrophy of the scalp. Alopecia, surprisingly, occurred in only 42% of the cases. The same may be said with respect to atrophy of the scalp. In our analysis the triad was found in only 40%. Thus, it is evident that presence of the triad is not essential for the diagnosis of lichen planopilaris (Table 1).

The duration of the disease varied from six months to 10 years. In fully 50% of the cases it was between six months and two years. The age distribution shows that it is not a disease of the young. Seventy per cent of the patients were between the ages of 30 and 70 years (Table 2).

From the literature one gains the impression that the disease is sex-linked. An analysis of the cases in which sex is mentioned shows 37% in males and 63% in females; that is, the disease is approximately twice as common in females. The reason for this is not clear.

CONTROVERSIAL FEATURES OF THE DISEASE

A. *Nomenclature.*—Through the years the disease has been reported under some 30 titles, each an effort to reflect the character of the disease as the authors conceived it. After due consideration, it is our belief that the simple yet inclusive title covering the outstanding features of the disease is follicular lichen planus. This will become evident from the discussion which ensues.

B. *Spinous Lesions (Spinulosismus).*—In the early days British authors especially focused their attention on the spinous features so characteristic of this disease. Since spinous lesions do not limit themselves to this disorder, it is easy to see why unrelated spinous diseases were responsible for much confusion. There are, of course, many diseases that have spinous elements in their make-up. They can roughly be divided into two groups:

1. Those in the first group are associated with other clinical entities, such as lichen scrofulosorum, follicular syphilis, pityriasis rubra pilaris, the trichophytids, and others. In these diseases no difficulty should be experienced in the diagnosis, since other features of the named diseases readily identify them as distinct from follicular lichen planus.

2. This group includes keratosis pilaris, lichen spinulosus, and phrynoderma. This group cannot always be readily excluded on purely clinical grounds, since about one-third of the cases of lichen planopilaris begin with spinous lesions and other features may be practically identical. However, the age of the patient, the course, and especially the pathological changes distinguish these from follicular lichen planus.

With respect to lichen pilaris seu spinulosus (Crocker), there are many recorded cases in which the spinous lesions were preceded by "folliculitis decalvans." This significant observation points to the view that many recorded instances of this disease may have been cases of follicular lichen planus.

C. *Atrophy.*—Atrophy constitutes a highly controversial feature of follicular lichen planus. Pringle failed to observe atrophy of the scalp and apparently did not think of it as a related feature. Little first stressed the scalp atrophy and brought it into proper relationship to the disease. McCafferty also agreed that the lesions of the scalp terminate in atrophy. Atrophy was an important factor in his interpretation of the disease as a form of ulerythema ophryogenes. Feldman indicated that atrophy is an essential feature of the disease and that both the spinous and the lichen planus lesions of the glabrous skin and scalp terminate in atrophy. However, W. Sachs and DeOreo found clinical atrophy, but no histologic proof of this.

Faced with these contradictory interpretations, we pose the following questions: 1. Is the atrophy clinical, histologic, or both? 2. Is the atrophy primary or secondary? 3. Is atrophy an essential part of the disease?

Points 1 and 2 are discussed under pathological aspects. With respect to Point 3, the analysis of the recorded cases shows that clinical atrophy is present in only 40% of the cases. Hence, while frequently observed, it cannot be considered an essential part of this syndrome.

PATHOLOGICAL ASPECTS

The histopathologic picture of follicular lichen planus is essentially that of lichen planus, but the characteristic changes involve the follicles and perifollicular areas. At times microscopic evidence of lichen planus in nonfollicular areas, in addition to follicular lichen planus, is present in the same sections. The typical microscopic observations were recorded in Case 1 and need not be repeated.

The question of atrophy in this entity requires histopathologic interpretation. The term "atrophic" is frequently used in the description of follicular lichen planus, particularly in reference to scalp lesions. It should be stressed that atrophy is usually a clinical designation and does not necessarily apply in the pathological sense.

Atrophy, as it is generally understood, is a loss or diminution in size or quantity of a tissue which cannot be regenerated. It is not a temporary process, but one that is permanent. Thus, it would be inaccurate to use the term atrophy when one refers to a thin epidermis, since thinning in itself does not necessarily mean permanent damage, as such tissue, potentially at least, can regenerate.

Feldman in two of his cases based the atrophy on fragmentation and diminution of the elastic tissue. These changes, he stated, were present not only in the affected skin but in the uninvolved as well. However, Feldman failed to mention details of such changes as would allow the conclusion of the presence of atrophy. Moreover, he failed to mention whether the loss of the elastica occurred in areas of cellular infiltration, under which condition it is an expected finding.

W. Sachs and DeOreo failed to detect definite histologic evidence of atrophy. Furthermore, they found that the elastic tissue changes in the affected area corresponded with those seen in a controlled series of classical cases of lichen planus without clinical atrophy.

In our Case 3, the scalp lesions, which were of two years' duration, showed active follicular involvement in apparently clinically advanced atrophic areas of the scalp, a finding also recorded by W. Sachs and DeOreo. In our Case 4, showing clinical follicular lichen planus of the body, the microscopic picture of the scalp conformed with the classical description of the pathology of alopecia cicatrisata (pseudopelade), since practically no follicles were present. Five years previously, the scalp in this case showed clinical features of follicular lichen planus, not confirmed, however, by microscopic study. These findings give us good reason to assume that Case 4 is a "burned out" example of follicular lichen planus. In view of this, we can assume that the end-stage of the scalp lesions in this disease and that observed in alopecia cicatrisata show similar pathological changes. This tends to corroborate the impression that at least some of the cases of alopecia cicatrisata are, in fact, end-states of follicular lichen planus.

Pierini and Borda,[13] in a recent study entitled "Pseudopelade and Lichen Planus" lend support to this view. They maintain that there is an intimate connection among lichen planus in all its clinical forms, lichen spinulosus, and pseudo-

13. Pierini, L. E., and Borda, J. M. C.: Pseudopelade and Lichen Planus: Is Pseudopelade a Form of Lichen Planus? Rev. argent. dermatosif. **33**:45, 1949.

pelade. Moreover, they state that "Graham Little's syndrome and Brocq's pseudopelade would merely be varieties of localization or evolutionary stages in the lichenian process."

Thus, the question raised previously, Is follicular lichen planus an atrophic disease?, divides itself into a consideration of (1) the elastica and (2) the pilosebaceous apparatus. In our cases the elastica shows surprisingly little change. Between the adnexal structures it is relatively normal. It is absent in the areas of cellular infiltration, and this is very likely due to displacement. Such displacement is common in all inflammatory processes, and, as in other dermatoses of this nature, restitution to the normal can be expected with the disappearance of the infiltrate. Accordingly, in the sense of elastic tissue changes, there is no atrophy in this disease.

The clinical atrophy observed in this disease is due to the loss of the pilosebaceous apparatus. At a glance, the absorption of the pilosebaceous structure may seem inadequate to produce the amount of atrophy seen in these cases clinically, but the rich follicular nature of the scalp must be taken into consideration.

We feel that the loss of the pilosebaceous structures is secondary in nature and is due to pressure of the perifollicular inflammatory reaction combined with counterpressure produced by the hyperkeratotic plugging of the dilated follicle, thus interfering with the blood supply.

SUMMARY

This study is based upon 4 personal observations and an analysis of 101 cases culled from the literature. The clinical picture presents a combination of the following features: lesions of lichen planus, spinous lesions, and alopecia of the scalp, frequently showing clinical atrophy; the triad is not essential for diagnosis.

The pathological picture is that of lichen planus involving the follicle and perifollicular areas and is diagnostic for the disease.

The atrophy is due to the loss of the pilosebaceous apparatus and does not depend upon the loss of elastic tissue. The atrophy is secondary in nature and is due to mechanical interference with the blood supply to the follicles.

Follicular lichen planus is the name that most appropriately expresses the clinical and pathological features of the disease.

290 West End Ave. (Dr. Silver).

1 W. 85 St. (Dr. Chargin).

55 E. 86 St. (Dr. Sachs).

USE OF A CYCLOHEXIMIDE MEDIUM FOR ISOLATION OF DERMATOPHYTES FROM CLINICAL MATERIALS

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CHAMBLEE, GA.

THE ISOLATION of dermatophytes from clinical materials frequently is complicated by contamination of culture tubes with bacteria and saprophytic fungi. Such specimens as human toenails and the hairs of domestic animals offer a special problem, owing to the presence of large numbers of these contaminants.

Bacterial contaminants are generally controllable by the use either of an acid medium, such as Sabouraud dextrose agar at pH 5.5, or of antibacterial antibiotics, or both. Sabouraud dextrose agar at pH 5.5 fortified with penicillin (20 units per milliliter) and streptomycin (40 units per milliliter) has been used routinely at the Mycology Laboratory of the Communicable Disease Center for the isolation of dermatophytes from clinical materials. The frequent occurrence of saprophytic fungi, however, necessitates inoculation of a large number of tubes for each specimen, and repeated subcultures often are needed to separate a suspected dermatophyte colony from growths of the more rapidly developing saprophytes.

On the basis of the findings of Leach and co-workers,[1] Whiffen,[2] Phillips and Hanel,[3] Fuentes and colleagues,[4] and studies in this laboratory on a selective medium for the isolation of Coccidioides immitis,[5] the antibiotic cycloheximide (Acti-Dione) was incorporated into our routine Sabouraud-penicillin-streptomycin agar in an effort to obtain a medium which would inhibit both bacterial and saprophytic fungus growth, and yet allow the isolation of dermatophytes.

MATERIALS AND METHODS

In preliminary studies, strains of all the common dermatophytes grew well on Sabouraud-penicillin-streptomycin agar to which had been added as much as 0.5 mg. of cycloheximide per milliliter. Two weeks following inoculation of the Sabouraud-penicillin-streptomycin agar and two sets of the same medium to which had been added 0.1 and 0.5 mg. of cycloheximide per milli-

From the Communicable Disease Center, United States Public Health Service, Department of Health, Education and Welfare, Atlanta, Ga.

1. Leach, B. E.; Ford, J. H., and Whiffen, A. J.: Actidione, an Antibiotic from Streptomyces Griseus, J. Am. Chem. Soc. **69**:474, 1947.

2. Whiffen, A. J.: The Production, Assay, and Antibiotic Activity of Actidione, an Antibiotic from Streptomyces Griseus, J. Bact. **56**:283-291, 1948.

3. Phillips, G. B., and Hanel, E.: Control of Mold Contaminants on Solid Media by the Use of Actidione, J. Bact. **60**:104-105, 1950.

4. Carmona de la Fuentes, A.; Trespalacios, F.; Fernández Baquero, G., and Aboulafia, R.: Effect of Actidione on Mold Contaminants and on Human Pathogens, Mycologia **44**:170-175, 1952.

5. Georg, L. K.; Ajello, L., and Gordon, M. A.: A Selective Medium for the Isolation of Coccidioides Immitis, Science **114**:387-389, 1951.

liter, respectively, no difference among the three media with respect either to amount of growth or to gross morphology of the following dermatophytes could be detected: Trichophyton mentagrophytes, Trichophyton rubrum, Trichophyton tonsurans, Trichophyton violaceum, Trichophyton verrucosum,[6] Microsporum audouini, Microsporum canis, Microsporum gypseum, and Epidermophyton floccosum.

The suppressive activity of cycloheximide against a variety of saprophytic fungi has been reported by Whiffen [2] and confirmed in this laboratory.[5]

An evaluation of the use of cycloheximide in the isolation of dermatophytes from clinical materials was undertaken. Two types of clinical materials were chosen for this experiment: (1) clippings of human toenails showing signs of onychomycosis, and (2) hairs from suspected ringworm lesions on cattle. Both of these materials, particularly the latter, usually are heavily contaminated with both bacteria and saprophytic fungi.

Sabouraud dextrose agar at pH 5.5 fortified with penicillin (20 units per milliliter) and streptomycin (40 units per milliliter) was selected as a control medium. The same medium to which had been added 0.1 mg. of cycloheximide per milliliter was the test medium. Cycloheximide stock solutions were prepared in aqueous potassium dihydrogen phosphate (M/15), sterilized by filtration, and stored at 5 C. Cycloheximide is soluble in water in amounts up to 2%, and solutions retain their antibiotic activity for at least six weeks at pH 3 to 5 when refrigerated. Measured quantities were added to sterilized, melted, and partially cooled Sabouraud dextrose agar in combination with penicillin and streptomycin.

I. ISOLATION OF DERMATOPHYTES FROM HUMAN TOENAILS

Nail clippings from 20 persons with suspected onychomycosis were collected in sterile containers. Through the courtesy of Dr. H. M. Janney, specimens were obtained from inmates of the Federal penitentiary in Atlanta by Dr. Libero Ajello. The clippings from each patient were cut into many small pieces, two or three fragments of which were inoculated into each of 12 agar slants—6 tubes of the control Sabouraud-penicillin-streptomycin agar, and 6 tubes of the same medium to which had been added 0.1 mg. of cycloheximide per milliliter. Tubes were incubated at 25 C. and examined after 5, 10, and 21 days. The amounts of saprophytic fungus growth was recorded at each reading, and any suspected dermatophyte colony was subcultured to a fresh slant of the same medium unless it appeared in pure culture, in which case it was allowed to develop on the original tube.

Results.—Table 1 indicates that of 120 tubes of Sabouraud-penicillin-streptomycin agar 16 showed dermatophytes, while of 120 tubes of the same medium to which cycloheximide had been added 44 showed dermatophytes. On the control medium, only 2 tubes yielded dermatophytes in pure culture and in 14 dermatophytes were isolated by subculture from the original tubes. On the cycloheximide medium, on the other hand, 30 of the 44 isolates were obtained in pure culture, and subculturing was required in only 17 cases. In two instances multiple dermatophyte infections were indicated by the development of more than one species in a single series of tubes. From Specimen 5, T. rubrum and T. mentagrophytes were isolated, each in pure culture on cycloheximide tubes. From Specimen 11, three dermatophytes, T. rubrum, T. mentagrophytes, and T. tonsurans, developed side by side on a single tube of the cycloheximide medium.

6. Trichophyton verrucosum has recently been validated by Ainsworth and Georg (Nomenclature of the Faviform Trichophytons, Mycologia, to be published) as the correct name for the dermatophyte more commonly known to both mycologists and dermatologists under the following species designations: faviforme, album, discoides, and ochraceum.

TABLE 1.—*Isolation of Dermatophytes from Human Toenails: Comparison of Results with Sabouraud-Penicillin-Streptomycin Agar, With and Without Cycloheximide*

	6 Tubes Without Cycloheximide		6 Tubes With Cycloheximide	
Specimen No.	No. of Tubes with Dermatophytes *	Species Isolated	No. of Tubes with Dermatophytes *	Species Isolated
1	1 (1)	T. mentagrophytes	2 (1)	T. mentagrophytes
2	0	.....	1 (1)	T. mentagrophytes
3	1	T. rubrum	3	T. rubrum
4	1 (1)	T. mentagrophytes	2 (2)	T. mentagrophytes
5	2	T. rubrum	6 (4)	T. rubrum—5 T. mentagrophytes—1
6	2	T. mentagrophytes	3 (3)	T. mentagrophytes
7	0	.....	0	.....
8	0	.....	0	.....
9	0	.....	0	.....
10	0	.....	6 (2)	T. mentagrophytes
11	2	T. rubrum	6 (2)	T. rubrum—6 T. mentagrophytes—1 T. tonsurans—2
12	1	T. mentagrophytes	4 (4)	T. mentagrophytes
13	0	.....	0	.....
14	6	T. mentagrophytes	6 (6)	T. mentagrophytes
15	0	.....	0	.....
16	0	.....	0	.....
17	0	.....	1 (1)	T. mentagrophytes
18	0	.....	1 (1)	E. floccosum
19	0	.....	1 (1)	E. floccosum
20	0	.....	2 (2)	T. mentagrophytes
Totals	16		44	

* Numbers in parentheses signify numbers of tubes in which dermatophyte was isolated in pure culture.

TABLE 2.—*Isolation of Dermatophytes from Human Toenails: Comparison of Development of Saprophytes on Sabouraud-Penicillin-Streptomycin Agar With and Without Cycloheximide*

	6 Tubes Without Cycloheximide		6 Tubes With Cycloheximide	
Specimen No.	Saprophyte Contamination *	Isolated Dermatophytes	Saprophyte Contamination *	Isolated Dermatophytes
1	1	1	1	2
2	4	0	1	1
3	4	1	1	3
4	1	1	0	2
5	2	2	0	6
6	1	2	0	3
7	2	0	0	0
8	5	0	0	0
9	1	0	0	0
10	6	0	0	6
11	3	2	0	9
12	2	1	0	4
13	1	0	0	0
14	1	6	0	6
15	3	0	0	0
16	1	0	0	0
17	6	0	0	1
18	6	0	0	1
19	0	0	0	1
20	5	0	1	2
Totals	55	16	4	47

* Number of tubes in which more than one-half of slant was covered with saprophyte growth by the 10th day.

Mixed dermatophyte infections have been reported previously. Tanissa [7] cited 91 cases of mixed infection of the scalp and 145 cases of multiple infections of the skin surface. Recently, Wooldridge [8] described a case in which three species were obtained upon multiple cultures from different areas of the body.

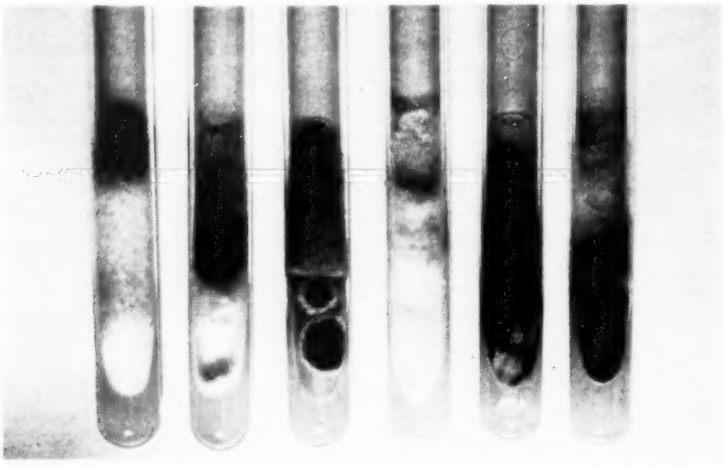

Fig. 1.—Penicillin-streptomycin medium (control medium) inoculated with toenail fragments from Specimen 10. All tubes were covered with saprophytic fungi by the 10th day. No dermatophytes were recovered.

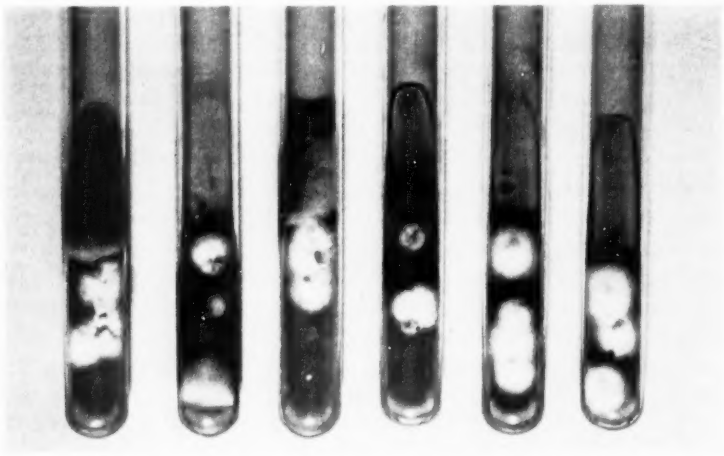

Fig. 2.—Cycloheximide-penicillin-streptomycin medium inoculated with toenail fragments from same specimen as in Figure 1. Colonies of Trichophyton mentagrophytes appeared on all tubes and are seen in pure culture in the last two tubes on the right.

7. Tanissa, A.: Tinea Tonsurans and Its Mixed Infection, Gaz. méd. port. **3**:385-392, 1950.

8. Wooldridge, W. E.: An Unusual Case of Multiple Fungus Infection, A. M. A. Arch Dermat. & Syph. **63**:633-635, 1951.

Table 2 indicates that the number of dermatophytes isolated paralleled the inhibition of the growth of saprophytic fungi by cycloheximide. In one case (Specimen 10) all six tubes of the control medium were completely covered with saprophytic fungus growth by the 10th day, whereas pure cultures of dermatophytes were obtained on all 6 of the corresponding cycloheximide tubes. In only 4 of 120 actidione tubes was more than half of the agar slant covered with saprophytic fungus growth by the 10th day. Figures 1 and 2 show typical sets of tubes containing control and test media after 21 days' growth.

II. ISOLATION OF DERMATOPHYTES FROM CATTLE HAIRS

Ringworm in cattle in the United States is due largely to T. verrucosum.[9] The isolation of this fungus from clinical materials is made difficult not only by the contamination of such materials with bacteria and saprophytic fungi but also by its

TABLE 3.—*Isolation of Trichophyton Verrucosum from Cattle Hairs: Comparison of Isolation of T. Verrucosum on Sabouraud-Penicillin-Streptomycin Agar, With and Without Cycloheximide and with Cycloheximide and Thiamine*

Specimen No.	6 Tubes Without Cycloheximide			6 Tubes With Cycloheximide			6 Tubes With Cycloheximide and Thiamine		
	Positive for T. Verrucosum	Negative*	Saprophyte Contamination†	Positive for T. Verrucosum	Negative*	Saprophyte Contamination†	Positive for T. Verrucosum	Negative*	Saprophyte Contamination†
1	0	0	6	4	2	0	5	1	0
2	6	0	0	6	0	0	6	0	0
3	1	2	3	3	3	0	2	4	0
4	0	0	6	3	2	1	4	0	2
5	2	0	4	6	0	0	6	0	0
6	0	0	6	1	3	2	2	4	0
7	2	0	4	6	0	0	5	0	1
8	2	0	4	6	0	0	6	0	0
9	0	0	6	4	0	2	5	1	0
Totals	13	2	39	39	10	5	41	10	3

* Number of tubes in which no dermatophyte developed and saprophytic contamination was either absent or minimal by the 10th day.

† Number of tubes in which more than one-half of slant was covered with saprophytic growth by the 10th day.

extremely slow development on the usual isolation media. Previous studies [10] have shown that the addition of thiamine to Sabouraud dextrose agar and incubation at 37 C. favor the development of T. verrucosum.

For this investigation, hairs from nine cases of suspected ringworm in cattle were cultured on six tubes each of (1) the control Sabouraud-penicillin-streptomycin medium, (2) the control medium plus 0.1 mg. of cycloheximide per milliliter, and (3) the control medium plus 0.1 mg. of cycloheximide and 0.5 γ of thiamine per milliliter. All tubes were incubated at 37 C. and examined after 5, 10, 21, and 28 days. The amount of saprophytic growth was recorded at each reading, and suspected dermatophyte colonies were subcultured to fresh tubes of the same medium unless they appeared in pure culture, in which case they were allowed to develop on the original tubes.

9. Fowle, L. P., and Georg, L. K.: Suppurative Ringworm Contracted from Cattle, Arch. Dermat. & Syph. **56**:780-793, 1947.

10. Georg, L. K.: The Relation of Nutrition to the Growth and Morphology of Trichophyton Faviforme, Mycologia **42**:683-692, 1950.

Although several dermatophyte species have been reported as causes of ringworm in cattle, only one species, T. verrucosum, was obtained from the nine specimens of cattle hair studied. The specimens had come from various parts of the United States: Alabama, Georgia, Michigan, Missouri, New York, and Pennsylvania.

Results.—Table 3 indicates the results of this experiment. Of 54 tubes of the control Sabouraud-penicillin-streptomycin agar inoculated, colonies of T. verrucosum developed on 13. Of the 54 tubes of control medium plus cycloheximide, 39 showed this organism, and, of 54 tubes of the control medium plus cycloheximide and thiamine, the organism developed on 41. Although there was no significant difference in the number of isolates of T. verrucosum on the thiamine-enriched and unenriched cycloheximide media, the fungus colonies appeared earlier on the thiamine medium —usually by the 6th day—and were well developed by the 14th day. On the unenriched cycloheximide medium, the colonies usually did not appear until the 14th day and were subcultured with some difficulty from among the saprophytes which were beginning to spread over the slants. A study of the table shows that the number of isolations of T. verrucosum paralleled the degree of inhibition of the growth of saprophytic fungi by cycloheximide. In many cases pure cultures of T. verrucosum were obtained on the cycloheximide tubes.

COMMENT

In a series of cultures of material from lesions suspected to be onychomycosis on a routine medium with and without the addition of cycloheximide, three times as many isolates of dermatophytes were obtained on the cycloheximide medium, and more than half of these were obtained in pure culture. The macroscopic and microscopic appearance of the isolates on the cycloheximide medium was identical with that on Sabouraud dextrose agar.

This ease of identification is an advantage over other selective media, such as Littman's ox-gall agar,[11] which so alters the gross and microscopic morphology of the dermatophytes that often they are difficult to distinguish from saprophytes and frequently must be subcultured to a more routinely used medium before they can be identified.

Although cycloheximide is still a comparatively expensive antibiotic, the amount required for use in the medium described is so small that the present cost is only a few cents a tube, and the antibiotic could reasonably be used for routine work. Comparative studies are being carried out in the Mycology Laboratory of the Communicable Disease Center on the use of this cycloheximide medium in the routine isolation of dermatophytes from skin scrapings of the feet, as well as from other materials often highly contaminated with saprophytic fungi. Preliminary results indicate the superiority of cycloheximide medium over all other media tested.

The reports of isolation of dermatophytes from animal hairs are relatively few, perhaps because these hairs are often so heavily contaminated with saprophytic fungi. The series of cultures of cattle hairs on cycloheximide medium with and without the addition of thiamine indicates that this antibiotic may be useful for such isolations.

11. Littman, M. L.: Growth of Pathogenic Fungi on a New Culture Medium, Am. J. Clin. Path. **18**:409-420, 1948.

SUMMARY

Sabouraud dextrose agar fortified with penicillin, streptomycin, and cycloheximide (Acti-Dione) was found to be of great value for the isolation of dermatophytes from clinical materials. It is of special value in cases in which the material to be cultured is heavily contaminated with bacteria and saprophytic fungi.

The addition of these antibiotics does not inhibit the growth of the dermatophytes studied or alter their morphological characteristics from those usually seen on Sabouraud dextrose agar.

In a series of cultures from 30 persons with suspected onychomycosis, three times as many dermatophyte isolates were obtained on a cycloheximide medium as on a similar medium without cycloheximide, and approximately half of the isolates on the cycloheximide medium were in pure culture.

Likewise, in a series of cultures from nine cases of suspected ringworm in cattle, three times as many dermatophyte isolates were obtained on a cycloheximide medium as on a similar medium without cycloheximide. T. verrucosum (T. faviforme, T. album, T. discoides, T. ochraceum) was the only dermatophyte isolated from the cattle hair. The addition of thiamine to the cycloheximide medium accelerated the growth of saprophytic fungi in the cycloheximide tubes of both series.

The number of dermatophytes isolated paralleled the degree of inhibition of the growth of saprophytic fungi in the cycloheximide tubes of both series.

Triple dermatophyte infection of the toenails was observed in one patient. The dermatophytes isolated in this case were T. mentagrophytes, T. rubrum, and T. tonsurans.

OBSERVATIONS ON ANTICOMPLEMENTARY REACTIONS

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LOS ANGELES

THE ANTICOMPLEMENTARY reaction is the inhibition of hemolysis in the antigen-free mixture of serum and complement used as control in complement-fixation tests. Such a serum is not suited for a Wassermann or a Kolmer test.

In dealing with anticomplementary reactions, one must differentiate between extrinsic and intrinsic anticomplementary reactions.

1. The "extrinsic" (or "exogenous" or "artificial") anticomplementary reaction is usually caused by bacterial or chemical contamination. Use of old sera and impurities, e.g., acids, alkalis, anticoagulants (oxalates, citrates, heparin), arsenicals, tannin, alcohol, etc., may provoke anticomplementary reaction in any serum.[1] All these extrinsic anticomplementary reactions can be avoided by proper laboratory technique.

2. The "intrinsic" (or "endogenous" or "autonomous" or "natural") anticomplementary reaction is not caused by faulty laboratory technique and cannot be avoided by correct laboratory technique but is an intrinsic quality of the serum itself.

A test for differentiating these two groups is the reproducibility of the anticomplementary reaction. If an anticomplementary reaction is noted, and the complement-fixation test repeated in the next day or two with fresh serum, proper ingredients, and correct technique again results in the anticomplementary reaction, the reaction can be considered intrinsic; otherwise, it belongs in the first group—that of the extrinsic anticomplementary reactions.[2]

PRESENT STUDY

I reviewed the charts of 144 patients who at one time or another had had anticomplementary reactions. All these anticomplementary reactions probably belonged in the intrinsic group. The complement-fixation tests were all done in the two largest serologic laboratories of the city, some of them at the Laboratory of the Los Angeles County General Hospital, most of them at the Central Laboratory of the Los Angeles City Health Department. Both these laboratories perform several thousand serologic tests for syphilis per month. The ingredients and technique used are well standardized; the personnel is well trained

From the Venereal Disease Clinic, Southeast Health Center, Los Angeles City Health Department.

1. Orsós, E. J.: Einfluss der Fehler bei der Blutentnahme auf die Serum-Reaktionen, München. med. Wchnschr. **83**:1745 (Oct. 23) 1936.

2. Olhagen, B.: Studies on Thermostabile Anticomplementary Human Sera, Acta med. scandinav., Supp. 162, p. 1, 1945.

and experienced; the performance is uniform. We assume, therefore, that the reported anticomplementary reactions are usually intrinsic and not caused by faulty laboratory technique.

Tables 1, 2, and 3 show distribution according to sex, race, and age of the total 144 patients.

The sexes and races are represented in our series with anticomplementary reactions in approximately the same proportion as in our average patient load.

TABLE 1.—*Distribution According to Sex*

Sex	No. of Patients
Female	77
Male	67
Total	144

TABLE 2.—*Distribution According to Race*

Race	No. of Patients
White	17
Nonwhite	127
Total	144

TABLE 3.—*Distribution According to Age*

Age, Yr.	No. of Patients
Up to 10	2
11 to 15	12
16 to 20	20
21 to 25	20
26 to 30	22
31 to 35	15
36 to 40	12
41 to 50	27
51 to 60	9
Over 60	5
Total	144

In Table 3 the first two groups (up to age of 15) show heavier representation in the anticomplementary reaction series than does our average patient load. This conforms with the heavier participation of congenital syphilis in our series with anticomplementary reactions (Table 5).

We considered patients "nonsyphilitic" if there was no history of syphilitic lesions, of positive serologic tests, or of antisyphilitic treatment, and physical examination did not reveal evidence of syphilis. In these patients the serologic tests were negative, except for anticomplementary reaction.

In the "probably syphilitic" group belonged patients without history of syphilis, but in whom the serologic tests—in addition to anticomplementary reaction—showed doubtful or positive Kahn, Mazzini, or complement-fixation reactions for syphilis on repeated examinations.

The further analysis of anticomplementary reactions occurring in syphilitic persons in regard to the stage of syphilis reveals that of the 127 syphilitics with anticomplementary reactions, there were 33 with the diagnosis of congenital syphilis and 94 with that of acquired syphilis.

Since the duration of infection in the majority of those with the latent disease could not be established accurately, we did not attempt to classify the cases further into early and late syphilis.

Of the total 144 patients with anticomplementary reactions, there were 33 with congenital syphilis. This means that in our series 22.9% of all anticomplementary reactions occurred in congenital syphilis. Of the 127 patients with syphilis in our anticomplementary reaction series, 25.9% had congenital syphilis.

TABLE 4.—*Distribution According to Syphilis Status*

Syphilis Status	No. of Patients	Percentage
Definitely syphilitic	127	88.2
Probably syphilitic	9	6.2
Nonsyphilitic	8	5.6
Total	144	100.0

TABLE 5.—*Distribution According to Stage of Syphilis*

Stage of Syphilis	No. of Patients	
Congenital		33
Latent congenital	27	
Central nervous system congenital	6	
Acquired		94
Primary	3	
Latent	67	
Central nervous system	21	
Cardiovascular	2	
Central nervous system and cardiovascular	1	

Cases of congenital syphilis comprise 3.92% of our total syphilis case load. This means that if syphilis cases would participate in the anticomplementary reactions in an unselected manner, regardless of stage, then congenital syphilis would represent about 3.92% of all syphilis cases. Since in our series with anticomplementary reactions congenital syphilis represented 25.9% and not 3.92% of all syphilis cases, it is evident that congenital syphilis participates in the anticomplementary series 6.6 times as often as expected.

Authors agree that anticomplementary reactions occur in syphilitics oftener than in persons not having syphilis. In 30,000 tests on a general hospital population, the incidence of anticomplementary reactions was seven times as great among syphilitics as it was among normal persons.[3] In our venereal disease clinic, where more cases of syphilis are seen than in a large general hospital population, this ratio

3. Eagle, H.: The Laboratory Diagnosis of Syphilis: The Theory, Technic, and Clinical Interpretation of the Wassermann and Flocculation Tests with Serum and Spinal Fluid, St. Louis, C. V. Mosby Company, 1937, p. 76.

is even higher. Our observations reveal the frequency of anticomplementary reactions by patients with congenital syphilis to be out of proportion. Anticomplementary reactions occur in congenital syphilis 6.6 times as often as expected if anticomplementary reactions were distributed equally among all stages of syphilis.

We wish to introduce a new concept, namely, the "repeatedly anticomplementary reaction." This is not identical with the above-mentioned reproducible anticomplementary reaction. The reproducible anticomplementary reaction is obtained one or two days after the first report of anticomplementary reaction and serves as a means of differentiating extrinsic from intrinsic anticomplementary reactions.

In our clinic, serologic tests for syphilis are routinely performed at certain intervals. Some of the 144 patients reviewed here showed the anticomplementary

TABLE 6.—*Distribution of Anticomplementary Reactions According to Source*

Source	No. of Patients
Blood	137
Spinal fluid	5
Blood and spinal fluid	2
Total	144

TABLE 7.—*Frequency of Anticomplementary Reactions in the Blood*

No. of Occurrences	No. of Patients
1	82
2	22
3	17
4	5
5	2
6	5
7	2
8	3
21	1*

* This patient was the subject of a special United States Public Health Service research project, and serologic tests for syphilis were repeated at frequent intervals for a long time.

reaction on only one occasion, others on several or many occasions in the course of many weeks, several months, and even years (Table 7). These repeated reactions occurred at least two or three weeks apart, usually months and sometimes years apart. If two anticomplementary reactions occurred in the same patient within two weeks, we considered it as a single anticomplementary reaction. For the reasons mentioned above, we considered all the anticomplementary reactions in our series as intrinsic. The "repeatedly anticomplementary reaction" means to us that the quality of the serum causing anticomplementary reaction is not transient but —even if temporary—lasts for a longer period, at least many weeks, usually several months, or even years. The "reproducibility" of the anticomplementary reaction, on the other hand, means the elimination of possible laboratory errors and verification of true intrinsic anticomplementary reactions at the same time.

The frequency of anticomplementary reactions in syphilis in general and in congenital syphilis in particular is more evident if considered in the light of the "repeatedly anticomplementary reaction."

In the spinal fluid the anticomplementary reaction occurred on only one occasion in each of the seven patients.

Of the total 144 patients, a single anticomplementary reaction in the blood occurred in 82 and "repeatedly anticomplementary reactions" in 57.

As stated previously, congenital syphilis comprises 3.92% of our syphilis caseload. In the series of "repeatedly anticomplementary reactions," congenital syphilis comprised 38.2% of all syphilis cases. In other words, congenital syphilis participated in our series of "repeatedly anticomplementary reactions" 10 times as frequently as expected, were anticomplementary reactions equally distributed among all stages of syphilis.

COMMENT

The nature of the intrinsic anticomplementary reaction is not well known. It probably is a nonspecific reaction due to an abnormal gamma globulin, a modified gamma globulin, an increase in normal gamma globulin, or to some other property.[4] But whatever its nature, all authors have agreed that it occurs in syphilitic sera

TABLE 8.—*Frequency of Repeatedly Anticomplementary Reactions in Same Case*

No. of Occurrences	No. of Patients	Syphilitic Status		
		Definite Syphilis	Congenital	Acquired
2	22	22	7*	15†
3	17‡	15	3	12
4	5	5	2	3
5	2	2	1	1
6	5	5	4§	1‖
7	2	2	2	..
8	3	3	2	1
21	1	1	..	1¶

* Two patients had central nervous system syphilis.
† One patient had central nervous system syphilis, and one had cardiovascular syphilis.
‡ Two patients had "probable syphilis."
§ One patient had central nervous system syphilis.
‖ This patient had central nervous system syphilis.
¶ This patient, the subject of a special research project, had primary syphilis.

several times as often as in nonsyphilitic sera. It is noteworthy that other authors emphasized that the anticomplementary reaction has no diagnostic implications and that no diagnostic significance is attached to such a laboratory report. Our series from a large venereal disease clinic revealed that 88.2% of anticomplementary reactions and more than 96% of "repeatedly anticomplementary reactions" occur in syphilitics. It should be stressed that although the anticomplementary reaction is nonspecific, its frequent occurrence in syphilitics warrants thorough examination and follow-up observation for syphilis. Especially is this true in cases of "repeatedly anticomplementary reactions."

Samples of "Repeatedly Anticomplementary Reactions" and Serological Behavior Patterns.—Some patients show an anticomplementary reaction on every occasion that a complement-fixation test for syphilis is obtained, the Kahn test at the same time being positive:

4. Davis, B. D.; Kabat, E. A.; Harris, A., and Moore, D. H.: The Anticomplementary Activity of Serum Gamma Globulin, J. Immunol. **49**:223 (Oct.) 1944.

R. S., a 17-year-old Negro girl, had a diagnosis of congenital syphilis. A test of the spinal fluid on Aug. 10, 1948, gave a negative reaction. She was treated with 6,000,000 units of penicillin in August, 1948. The tabulation shows results of blood serologic tests. *AC* indicates an anticomplementary reaction.

Date	4/15/48	4/29/48	5/13/48	6/10/48	9/23/48	10/25/48	11/22/48	5/5/49	9/14/50
Kahn	+	+	+	+	..	..	..	+	..
Kolmer	..	AC	AC	AC	AC	AC	AC	AC	AC

Some patients show an anticomplementary reaction on several occasions, but not on all occasions. Whenever the serum is not anticomplementary, the Kolmer test shows the highest titer. The anticomplementary reaction recurs from time to time, while the Kahn reaction is always positive:

A. D., a 16-year-old Negro girl, had congenital syphilis, with negative results on tests of the spinal fluid in June 1950. Treatment with 6,000,000 units of penicillin was given in July, 1950. Blood serologic tests gave the following results:

Date	5/18/50	6/23/50	7/26/50	8/24/50	10/27/50	12/29/50	1/9/51	5/17/51
Kahn	+	..	+	..	..	..	..	+
Kolmer	AC	AC	44444	AC	44444	AC	44444	AC

W. J., a 16-year-old Negro boy, had congenital syphilis. A spinal fluid reaction in July, 1950, was negative. Treatment with 6,000,000 units of penicillin was given in May and June, 1949. Results of blood serologic tests were as follows:

Date	4/25/49	5/2/49	5/12/49	8/8/49	11/17/49	8/1/50	1/8/51	7/24/51	1/3/52
Kahn	..	..	+	..	..	+	..	..	..
Kolmer	AC	AC	AC	AC	AC	4444	AC	44444	44444

In the following case the serum on three occasions showed the anticomplementary reaction, with the Kahn reaction at the same time positive. After treatment the serum was no longer anticomplementary, and the Kolmer reaction was of the highest titer.

D. D., a 55-year-old Mexican woman, had asymptomatic central nervous system syphilis. In April 1951, serologic tests in the spinal fluid gave positive results, but the fluid showed no spirochetal activity. Treatment with 9,000,000 units of penicillin was given in May, 1951. Blood serologic tests showed these results:

Date	4/10/51	4/25/51	5/9/51	6/6/51	2/14/52
Kahn	..	+	+	+	—
Kolmer	AC	AC	AC	44444	44444

In some cases the anticomplementary reaction persists or recurs from time to time for many years. In the following case the reaction persisted for at least 10 years.

J. B., a 30-year-old white man, had a verified history of antisyphilitic treatment in the United States Army in 1942-1943. In 1949 the spinal fluid reaction was negative. The diagnosis was late latent syphilis. Serologic tests gave the following results:

Date	12/1/41	6/21/49	7/11/49	6/5/51
Kahn	+	+	..	+
Wassermann	AC	AC	..	..
Kolmer	..	..	44440	AC

Finally, some cases show a rather atypical, unstable, and at times unreliable serologic course:

J. P., a 13-year-old Negro girl, had congenital syphilis. A negative spinal fluid reaction was obtained in Oct., 1948. Treatment with 6,000,000 units of penicillin was given in Nov., 1948. Results of serologic tests were as follows:

Date	4/22/48	4/29/48	10/14/48	10/9/51
Kahn	+	+	—	Doubtful
Kolmer	AC	AC	AC	44443

For N. B., a 39-year-old Negro man, the diagnosis was asymptomatic central nervous system syphilis. Positive reactions were obtained on serologic tests of spinal fluid in Aug., 1949, and June, 1950. On the former occasion spirochetal activity was noted, but on the latter inactivity was reported. He was treated with six injections of a bismuth preparation and 9,000,000 units of penicillin in 1949. Serologic tests gave the following results:

Date	7/18/49	7/27/49	8/15/49	5/25/50	6/7/50	3/15/51
Kahn	+	—	+	Doubtful	..	..
Kolmer	..	44444	AC	..	AC	AC
Wassermann	..	..	..	+	..	..

After this paper was prepared, we tried to secure Treponema pallidum immobilization (TPI) tests on the patients with repeatedly anticomplementary reactions. Of the 57 patients in this series, 17 could be brought to the clinic for this test. Of the 17 tests, 15 were reported positive, including that of 1 patient whom we classified as "probably syphilitic"; 1 blood specimen was "hemolyzed," and the treponemal immobilization test could not be repeated because the patient moved. One test was reported negative, but this patient has a verified history of adequate antisyphilitic treatment from 1941 to 1950.

SUMMARY

In a series of 144 patients with anticomplementary reactions, 88.2% occurred in syphilitic persons, for 25.9% of whom the diagnosis was congenital syphilis. Congenital syphilis participated in anticomplementary reactions about seven times as often as would be expected were anticomplementary reactions distributed equally among cases of congenital and acquired syphilis.

The concept of "repeatedly anticomplementary reactions" is presented. Of "repeatedly anticomplementary reactions" 96.5% occurred in syphilitic patients, 38.2% of whom had congenital syphilis. Congenital syphilis participated in the "repeatedly anticomplementary reactions" 10 times as often as expected.

Because of the heavy participation of syphilis in general and of congenital syphilis in particular in the anticomplementary reactions, thorough examination and serologic follow-up of persons with anticomplementary reactions should be made, especially of those with "repeatedly anticomplementary reactions."

UNUSUAL FORMS OF SOLAR DERMATITIS

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IN PREVIOUS publications by this group,[1] a tentative classification of the light-sensitive skin eruptions was formulated. The following working classification based on types of lesions was adopted: (1) plaque-like type, (2) contact eczematous type, (3) papular and prurigo-like types, and (4) erythematous type—erythema solare perstans.

The plaque-like form has been the subject of a previous publication,[1] presented in considerable detail.

The first patient to be reported on here had vesiculobullous and prurigo-like lesions with scarring, a peculiar yellowish-brown color, and a leathery texture. He did not have porphyria but had cirrhosis of the liver. Nékám [2] described a similar severe light-sensitive eruption in a farmer aged 37 in whom the disease developed at the age of 20. He had bullous lesions, pigmentation, and atrophy of the face and hands. There was no mention of liver disease.

The lesions of the second and third patients are not readily placed in the classifications listed. They probably should be with the group described and classified by Arnold [3] and Brunsting [4] as pseudocolloid milium. The condition is occasionally associated with other forms of solar dermatitis, it is wart-like, and we believe that the term verrucous solar dermatitis is more descriptive.

REPORT OF CASES

CASE 1.—E. H. B., a farmer-rancher of German extraction, aged 37, had a known sensitivity to sunlight at the age of 7, when his first skin lesions developed. The local physician, in southwest Texas, told the family that his light sensitivity and the brownish mottling of his teeth were due to the fluorine in the water and that several other people in the area were similarly affected.

Read before the Section on Dermatology and Syphilology at the One Hundred and First Annual Session of the American Medical Association, June 10, 1952.

1. Lamb, J. H.; Shelmire, B.; Cooper, Z.; Morgan, R. J., and Keaty, C.: Solar Dermatitis, Arch. Dermat. & Syph. **62**:1, 1950.

2. Nékám, L., Editor: Corpus iconum morborum cutaneorum, Leipzig, Johann Ambrosius Barth, 1938, Vol. 1, p. 81, and Vol 2, p. 305.

3. Arnold, H. L., Jr.: Colloid Pseudomilium: Review of Its Nomenclature and Report of Case, Arch. Dermat. & Syph. **48**:262, 1943.

4. Brunsting, L. A., and Mason, H. L.: Porphyria with Cutaneous Manifestations, Arch. Dermat. & Syph. **60**:66, 1949. O'Leary, P. A.; Montgomery, H.; Brunsting, L. A., and Kierland, R. R.: Chronic Porphyria with Cutaneous Manifestations, ibid. **62**:596, 1950.

When the patient was a child the lesions were erythematous and vesiculobullous, especially on the hands and arms. They developed with each exposure to warm sunlight and also following an ultraviolet light treatment. For the preceding 10 to 12 years, ulcers had formed instead of vesicles and bullae and lesions were more prominent on the neck and face. Individual lesions usually passed through stages of papule, ulcer, and scar. The patient also noticed that the skin generally had become progressively darker brown during the previous year. Libido decreased to an outlet of three to five times yearly.

The past history revealed that the patient had infectious jaundice when he was a child, influenza in 1918, and mumps with orchitis in 1947. He had moderate acne in his late teens. A brother and sister had skin that was light-sensitive but not to such an extreme degree. He drank an occasional bottle of beer but never more than three or four bottles a week.

Examination on Nov. 3, 1948, revealed a well-developed man with sclerae, skin, and mucous membranes slightly icteric. The skin of the face showed marked pitting and scarring, with

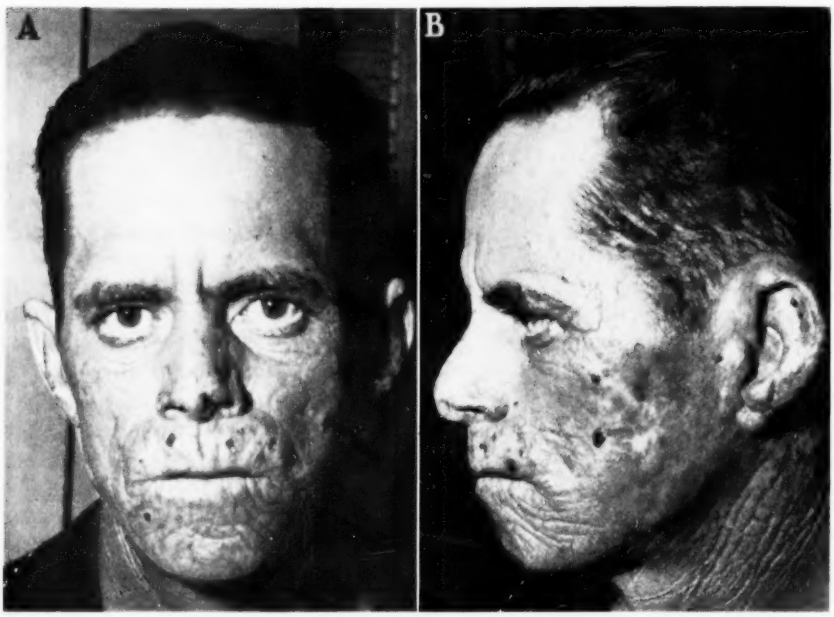

Fig. 1.—Patient 1 (E. H. B.).

rhagades that were deep about the mouth and less so about the eyes and nose. The skin was shiny, indurated, and yellowish-brown. Numerous ulcers in various stages of healing were present on the face, neck, and rims of the ears. A defect in the left nasal ala was the sequela of such an ulcer. A port-wine nevus 6 by 5 in. (15 by 10 cm.) in diameter was present on his back. The hands and arms showed no active lesions, but there were scars of previous ones. A decrease of axillary and pubic hair was noted. The patient was edentulous. His liver was enlarged to 3 fingerbreadths below the costal margin on the right side, but was smooth and nontender. The testes were abnormally small. Blood pressure was 120/60. Otherwise the examination was negative.

Laboratory results included negative serological tests for syphilis on three occasions. The van den Bergh reaction and icterus index increased progressively. The blood cholesterol was 319 mg. per 100 cc. A seminal count was 57,000,000 sperm cells per cubic centimeter (low); motility was 35%, with a volume of 2.25. Oleoresin patch tests followed by application of ultraviolet light revealed no photosensitizing properties for the various common weeds, flowers,

grasses, and trees native in the Southwest. A complete blood count, tests for blood protein and blood chloride, routine urinalysis, and x-rays of skull and kidneys were all normal. The urine specimens were always dark, but tests were negative for porphyrins. The urine was tested again at the Mayo Clinic, and Dr. Brunsting reported in November, 1948, and again in February, 1949, that it "showed no uroporphyrins or porphobilinogen." The total creatinines averaged 1,829,367 mg. in 24 hours, preformed creatinine averaged 1,717.57 mg. in 24 hours, creatine averaged 113.154 mg. in 24 hours, and 17-ketosteroids averaged 8.48 mg. in 24 hours.

Histologic examination of skin removed from the face showed parakeratosis and acanthosis, with plugging of pilosebaceous follicles. Atrophy of the epidermis was noted in some areas, but epidermal proliferation was predominant. Spongiosis and intracellular edema of prickle cells and liquefaction degeneration of basal cells were present in moderate degree. The corium showed basophilic degeneration with homogenization of connective tissue. A moderate diffuse lymphocytic infiltrate and endothelial proliferation of blood vessels were noted.

The patient was given anteron® (chorionic gonadotropin from pregnant mare's serum), 375 international units a day for five months, during which time his skin lesions improved an estimated 50 per cent, but laboratory data remained about the same. During this five months swelling of the abdomen developed, and an exploratory laparotomy was done in March, 1949. Cirrhosis with ascites was found. While fishing in October, 1949, the patient had a hemorrhage from esophageal varices and died suddenly.

CASE 2.—C. L. R., aged 26, a field worker for an oil company, had a known hypersensitivity to sunlight when he was 5 years old. He grew up at Healdton, in south-central Oklahoma, where the minimum fluoride content of ground water is over 1.5 parts per million. He was of German-Irish extraction. When he was a child the lesions were erythematous, with marked edema. A bluish-red suffusion was common, and ulcerations occurred over finger joints and ears. After he was grown up similar lesions appeared with exposure to summer sunlight, even if the light passed through window glass. Warm fluorescent lights and infrared lights were known to have caused reactions. Attacks were accompanied by irritability, nervous tension, and arthralgias. He had no children, and no contraceptives had been used in five years of married life. Libido was normal. He used alcohol socially but never excessively, and frequently he went months without it. Two older sisters had similar light sensitivity. The oldest sister had verrucous changes which the patient said were more severe than his.

Examination on March 6, 1948, showed verrucous crusting and exaggerated skin markings over the tips of the ears, on the dorsa of the hands, and to a less extent on the bridge of the nose. Scattered discrete milia were present on the cheeks.

Laboratory examination gave a seminal count of 31,000,000 sperm cells per cubic centimeter. Motility was decreased to 10%, and the total volume was 4 cc. The average urinary total creatinine was 1,444.0 mg. in 24 hours, preformed creatinine averaged 1,273.75 mg. in 24 hours, creatine averaged 170.3 mg. in 24 hours, and 17-ketosteroids averaged 12.29 mg. in 24 hours. The results of sulfobromophthalein (bromsulphalein®) tests on three occasions ranged from 0 to 5% retention in 45 minutes. Serological tests for syphilis, complete blood counts, and urinalyses on at least three occasions were normal. Urinary porphyrin determinations at the Mayo Clinic in January and March, 1949, were reported as showing no uroporphyrins or porphobilinogen. Oleoresin patch tests followed by ultraviolet light showed no photosensitizing properties in weeds, grasses, flowers, and trees. In addition, the patient was given ultraviolet light following the application of several petroleum products, and it was found that none contained photosensitizing properties for him at that time. Tests with Foto-Flood, cold quartz (Mediquartz 410 Spot Irradiator), and hot quartz lamps caused no more reaction than on a normal control. A passive transfer test with the patient's serum was negative.

Histologic examination of skin from the hand showed atrophy alternating with areas of acanthosis. Hyperkeratosis was excessive, with plugging of hair follicles. A few areas of intercellular edema of basal cells was present. The dermis showed edema, dilated blood vessels, and lymph spaces. Marked vascular endothelial proliferation and hypertrophy were the most significant changes. Some homogenization of collagen was noted in the upper dermis. Special stains showed acid polysaccharides to be normal, but neutral polysaccharides were excessive in the epidermis and in the dermis. An attempt with special stains to show porphyrins in the skin was unsuccessful.

The patient was given anteron,® 500 international units daily, for approximately four months. He improved during the winter months while not receiving therapy, and he had no severe reactions in the summer. No change in status could be attributed to the treatment.

Case 3.—L. G., a man aged 45, a lake custodian, had resided about Shawnee, in central Oklahoma, all his life. When he was a child he had lesions of the hands which he described as being 2 to 3 mm. flesh-colored papules on the dorsa of thumbs, fingers, and webs. They seemed to increase in size each summer, but erythema was not noticed until 1948, when he was 42 and sunlight hypersensitivity developed. Hypersensitivity first was manifested by stinging, redness, and thickening of the skin anterior to the ears and also on the hands. He had jaundice of unknown cause in 1948. The patient was a confirmed alcoholic and drank 1 pt. (0.5 liter) of liquor daily in 1951. Libido had decreased so that outlet was only six to eight times yearly. He was the only member of his family to have light-sensitive skin. He had no children and his marriage had lasted only 14 days.

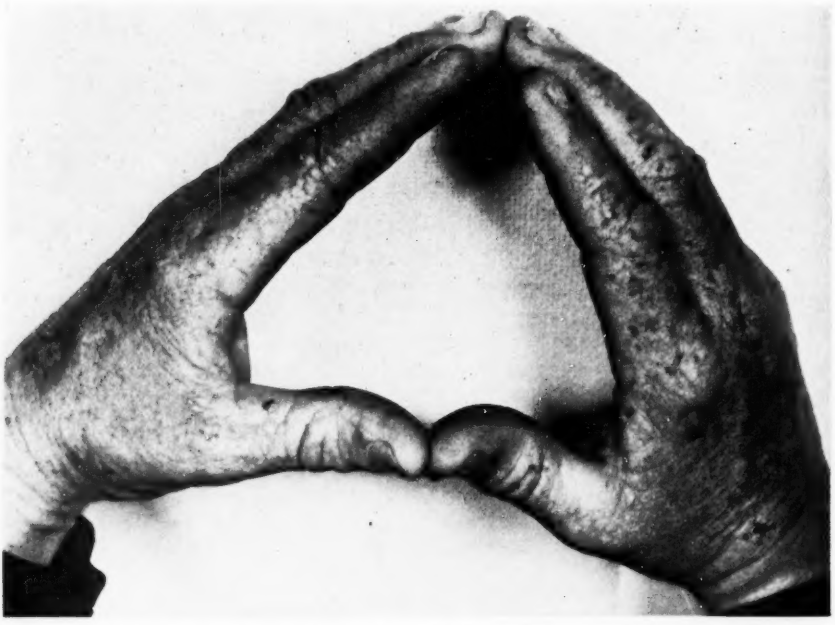

Fig. 2.—The hands of Patient 3, showing verrucous solar dermatitis.

Examination on Aug. 8, 1951, showed lesions over the malar prominences extending to both preauricular areas. These were erythematous, indurated, and plaque-like, with mild superficial scaling. Vesiculation was absent. On both hands, particularly on the dorsa of thumbs and index fingers, there were solitary, nodular, verrucous lesions and exaggerated skin markings. Physical examination otherwise was negative.

Laboratory tests included a negative Wassermann reaction and a negative sulfobromophthalein test (0 retention in 45 minutes). A total seminal count was 12,000,000 per cubic centimeter. Volume was 4 cc., and motility was 0.

A biopsy specimen from the left hand was prepared with several special stains by Dr. Walter Joel [5] and reported on by him as follows:

5. Dr. Joel is associate professor of pathology at the University of Oklahoma School of Medicine. He formerly was associated as pathologist with A. Buschke at Rudolf Virchow Hospital, in Berlin.

1. Hematoxylin and eosin stain showed the cornified layer of the skin to be increased. There was hyperkeratosis but no parakeratosis. Edema of the basal layer was minimal. The dermis adjacent to the epidermis was poor in cells and was slightly edematous. In the middle layer of the dermis there was basophilic degeneration of the connective-tissue fibers.

2. Staining for fat with Congo red showed few deposits of fat granules in the connective-tissue components between the collagen fibers. Those fatty changes that were present were in the ground substance. Elastic fibers showed marked swelling, loss of continuity and fragmentation.

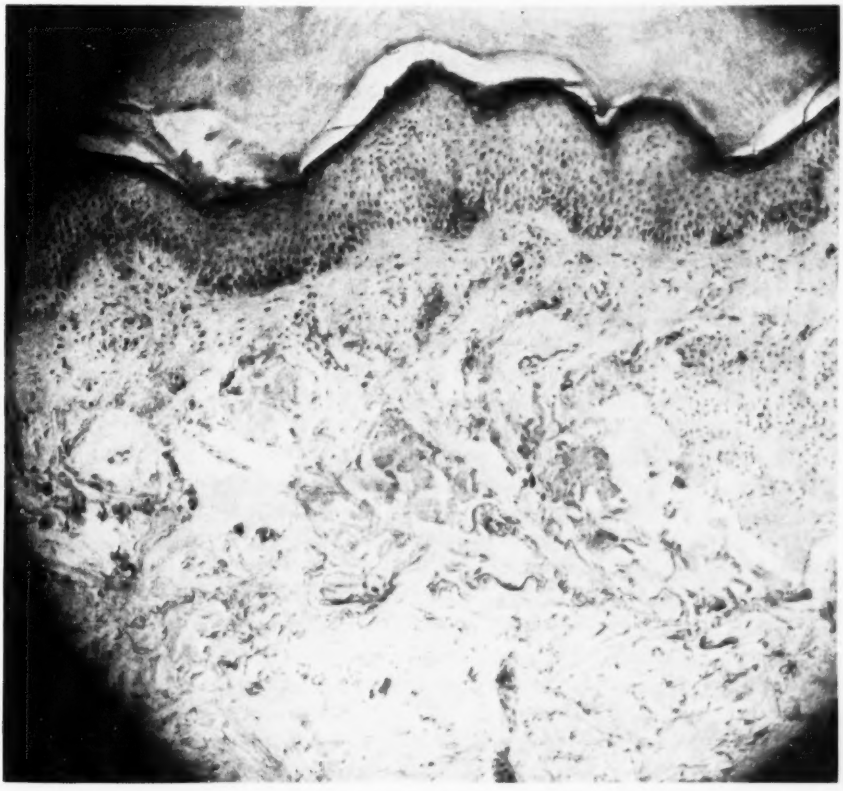

Fig. 3.—Hematoxylin and eosin stained section from the dorsum of the left hand of Patient 3.

3. The McManus stain for neutral polysaccharides revealed more or less circumscribed purplish-red areas in the upper dermis, representing an increase in neutral polysaccharides.

4. The Hale[6] stain for acid polysaccharides showed the presence of a more or less homogeneous material, staining deep-bluish between the collagen fibers, which were counterstained with picrofuchsin and were colored red. The acid polysaccharides definitely were increased and could consist of hyaluronic acid or a sulfuric acid ester of mucin.

6. The Hale stain consists of a colloidal iron, for which acid polysaccharides show an affinity (Nature, London **157**:822, 1946). Various counterstains may be used to help distinguish collagen, nuclei, and elastic tissues from ground substance.

5. The fluorescent[7] stain showed below the epithelium a nonfluorescent region which corresponded to the cell-poor area. Below this tissue, broad collagen fibers were visible, presenting a light greenish fluorescence. These fibers corresponded to those which showed basophilic degeneration with the hematoxylin and eosin stain. The so-called ground substance was shown by the presence in excess of neutral and acid polysaccharides which stained somewhat yellowish or orange. Similar polysaccharides are seen in allergy and hypersensitivity lesions, such as the Aschoff body of rheumatic fever and the nodular lesions of periarteritis nodosa.

The patient improved progressively with anteron,[8] 500 international units daily, though he continued to drink some alcohol every day.

COMMENT

The diverse forms of the lesions manifested by light-sensitive patients do not appear to fall into any specific pattern as regards the distribution in time of occurrence. Erythema was present early in the disease or both early and late in all three patients. Bullous and vesicular lesions characterized the early phase in only one patient (Patient 1). Early ulcer formation had occurred in one, associated with pseudocolloid milia of verrucous type, while late ulcer formation was apparent in one patient. Verrucous lesions of late onset had occurred in one. Papular lesions had appeared at some time during the course of the disease in all. The lesions of all were made worse by exposure to sunlight.

Microscopically, the chief characteristics observed in all three were basophilic degeneration and homogenization of connective tissues, the basic change in the collagen being more extensive in Patients 2 and 3 than in Patient 1 and similar to that described in colloid milium. The acid and/or neutral polysaccharide content of the connective tissues was increased.

The possible role of steroids in the etiology and treatment of light-sensitive skin diseases was considered in a previous publication.[8] While there was a presumptive evidence of liver damage or disease in all on history or examination, such damage was proved by laparotomy and biopsy only in Patient 1. In this patient the extreme degree of liver disease, probably beginning with chronic hepatitis in early life, was responsible for the known sterility and low-grade androgen production, since the mumps orchitis had occurred only two years previously. However, the orchitis undoubtedly provided an additional hiatus in the patient's endocrine status.

In the presence of deranged liver function, profound changes in steroid inactivation may be anticipated. In general, the normal biological transformations undergone by the steroids in the body are probably not related to their utilization as such but are modes of inactivation; the so-called inactivation products only recently are being shown to have physiological effects in the body remotely removed from the effects of the precursors. The mechanism of "inactivation" also acts in regulating the quantities of circulating hormone and thus indirectly controls the production or release of tropic hormones from the pituitary. This situation is particularly significant in respect to the pituitary output of gonadotropins. The organs involved in the biological transformations are primarily the liver and, to a less extent, the kidneys.

7. The fluorescent stain requires an ultraviolet-irradiated stage to give the best effects. It is a secondary fluorescence of stains which are specific for certain tissues and chemicals. Berberine sulfate and primulin with thiasol may cause fluorescence with mucopolysaccharides. A counterstain with acridine is often desirable. Frozen sections or paraffin section are suitable.

8. Lain, E. S.; Lamb, J. H.; Keaty, C., and Hellbaum, A. A.: The Use of Steroid and Gonadotrophic Hormones in Hydroa Vacciniforme, South. M. J. **41**:1041, 1948.

Estrogen inactivation[9] is accomplished largely in the liver. In liver damage from any cause, the inactivation is decreased and the amount of circulating estrogen thereby increases.[10] Similarly in dietary deficiency, especially in thiamine deficiency and in the absence of dietary riboflavin, or in simple inanition, the amount of circulating free estrogen is increased.[11] As far as we are aware, the participation of trace elements in hepatic inactivation of steroids has not been studied.

Failure of estrogen inactivation and resultant rise in blood-free estrogen, by the back-flow mechanism, inhibits the production of pituitary follicle-stimulating hormone.[9b] Since follicle-stimulating hormone in the male is involved primarily in the initiation or maintenance of spermatogenesis (although androgen in small amounts is necessary), there may be seminal failure on the liver-estrogen-pituitary basis. Administered estrogen has been found to depress the production or release of pituitary follicle-stimulating hormone and further to cause the release of increased amounts of pituitary luteinizing hormone.[12] Androgen production by the testicular Leydig cells, which is dependent upon pituitary luteinizing hormone, may be curtailed by the direct action of estrogen on the testis.

Liver function and androgen inactivation are also intimately related. Androgen transformation involves the production of estrogen as an active product which may be recovered in the urine in increased amounts. It may therefore lead, on the one hand, to increased amounts of estrogen, again depressing pituitary follicle-stimulating hormone production. On the other hand, failure of androgen inactivation may lead to the presence of excess androgen, which is known to exert only a mildly inhibitory effect upon pituitary follicle-stimulating hormone production. In this instance, the high titers of androgen may cause seminal failure, since the effect of large amounts of androgen is depressing upon the germinal epithelium to arrest spermatogenesis. It may be seen that the degree and types of testicular failure may depend upon abnormal liver function in controlling the amounts of circulating hormone. The degree of seminal failure, decreased libido, sterility, decrease in 17-ketosteroid production, and sparsity of pubic and axillary hair in the patient under consideration can easily be related to the advanced cirrhosis.

In this patient, the blood cholesterol was significantly elevated (317 mg. per 100 cc.). Plasma cholesterol, especially ester cholesterol, falls in hepatocellular disease[13] and is elevated in obstruction of the common duct and in cholelithiasis.[14] Laparotomy in this patient showed the common duct to be normal and the gall bladder to contain little bile and to have thin walls. The biopsy specimen taken at operation was diagnosed as showing the hepatocellular type of cirrhosis.

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9. (*a*) Zondek, B.: Über das Schicksal des Follikelhormons (Follikulin) im Organismus, Skandinav. Arch. Physiol. **70**:133, 1934. (*b*) Lloyd, C. W., and Williams, R. H.: Endocrine Changes Associated with Laennec's Cirrhosis of the Liver, Am. J. Med. **4**:315, 1948.

10. Talbot, N. B.: Inactivation of Endogenous Estrogen by Liver, Endocrinology **25**:691, 1939.

11. Biskind, M. S., and Shelesnyak, M. C.: Effect of Vitamin B Complex Deficiency on Inactivation of Ovarian Estrogen in Liver, Endocrinology **30**:819, 1942.

12. Hellbaum, A. A., and Greep, R. O.: Action of Estrogen on Release of Hypophyseal Luteinizing Hormone, Proc. Soc. Exper. Biol. & Med. **63**:53, 1946. Funnell, J. W.; Keaty, C., and Hellbaum, A. A.: Action of Estrogens on Release of Luteinizing Hormone in Menopausal Women, J. Clin. Endocrinol. **11**:98, 1951.

13. Everett, M.: Medical Biochemistry, Ed. 2, New York, Paul B. Hoeber, Inc., 1946.

14. Bray, W. E.: Clinical Laboratory Methods, Ed. 4, St. Louis, C. V. Mosby Company, 1951.

While a basal metabolism test was not done on this patient, the elevated cholesterol may or may not have been due to hypothyroidism. It is, however, suggestive that in hypothyroidism the metachromatic ground substance of the corium (polysaccharide) is altered. The thyroidal-gonadal relationship need not be discussed here.

So far as the skin itself is concerned, the activity of steroids in maintaining the connective tissues and ground substance is of great importance. The action of these substances upon the connective tissues is probably effected by the catalytic activity of the hormones upon enzyme systems and their substrates. The definitive effects of androgen upon the connective tissues and the ground substance have been investigated. The collagenous fibers and fibrils of animals being treated with androgen (testosterone propionate) are coarser, mast cells are more numerous, and the ground substance appears to be increased.[15] Androgen (but not estrogen) has been found also to increase the collagen nitrogen and the numbers of connective-tissue fibers, as well as to increase the tensile strength of the connective tissues.[16] Estrogens, on the other hand, are known to influence actively the ground substance in water binding (not simple edema) and tend to the production of mucoid connective tissue.[17]

It should be pointed out, with respect to the effects of steroids on the ground substance, that their known effects upon nitrogen metabolism and electrolytes probably exert marked influence upon the cutaneous connective tissue and its elements. The electrolytes appear to act as ionized polymers in maintaining the normal polysaccharide (hexosamine) content of the tissue. For example, the water (extracellular) content and sodium (but not potassium) content in the comb of the cockerel are much higher than those present in the same tissues of the capon.[18] The substrates involved are probably hyaluronidase and/or chondroitin sulfate or some closely related substance.

The role of androgen in melanin production has been clarified by the important studies of Edwards, Hamilton, and associates.[19] When androgen is depressed, the production of melanin is depressed. Stokes and Beerman [20] reiterated the role of the sex steroids in tanning of the skin. With low levels of androgens in the skin, incomplete enzymal reactions in the tyrosine-to-melanin system may result in the formation of intermediate products and not mature (black) melanin. Because of the lack of black melanin in the basal cells of epidermis, strong sunlight is not filtered from the corium. Thus the dermal vessels and the collagen are subjected to abnormal amounts of actinic radiation, with resultant vesiculation, prurigo, induration, and verrucoid and plaque-like eruptions of solar dermatitis.

15. Hamilton, J. B.: Growth Changes Induced by Androgens in the Connective Tissues, Sebaceous Glands, Hairs, Muscle, and Melanoblasts of the Skin, Anat. Rec. **97**:340, 1947.

16. Herrick, E. H.: Tensile Strength of Tissues as Influenced by Male Sex Hormone, Anat. Rec. **93**:145, 1945.

17. Bachman, C.; Collip, J. B., and Selye, H.: Proc. Roy. Soc., London, s.B **117**:16, 1935.

18. Ludwig, A. W.; Chen, D. K., and Soffer, L. J.: The Relationship Between Connective Tissue Mucopolysaccharide Content and Tissue Electrolyte Composition, read before the thirty-fourth meeting of The Endocrine Society, Chicago, June 5, 1952, to be published.

19. Edwards, E. A.; Hamilton, J. B.; Duntly, S. Q., and Hubert, G.: Cutaneous Vascular and Pigmentary Changes in Castrate and Eunuchoid Men, Endocrinology **28**:119, 1941.

20. Stokes, J. H., and Beerman, H.: Photodynamic Effects in Dermatology, Am. J. M. Sc. **203**:608, 1942.

Little attention has been paid to the importance of trace elements in the various enzymal reactions of the body. It is interesting that two of our patients lived in areas where the fluoride content of the water was in excess of that advocated by the United States Public Health Service. Miller [21] emphasizes the necessity for various trace minerals for normal enzymal reactions; for example, catalases which protect the body from overoxidation have iron as the activating mineral component. Carbonic anhydrase, the enzyme having to do with the liberation of carbon dioxide from the lungs into the air, has zinc as its activating mineral element. Zinc is an essential factor in the functioning of alkaline phosphatase enzymes. It is reported that the white blood cells in leukemia are deficient in zinc content, in contrast to normal white cells. The cholinesterase enzyme is activated by manganese. The acetylase enzyme contains manganese and pantothenic acid. Vitamin B_1 has small amounts of cobalt in the molecule, and cobalt is considered an activating element in the action of this vitamin.

Lerner and Fitzpatrick [22] emphasize the fact that copper is essential for normal pigmentation in mammals and is required in tyrosinase activity. The addition of trace amounts of copper salts to a deficient diet restores pigmentation. It is a well-understood fact among animal breeders that the lack of vital trace elements will cause serious weaknesses in muscle and bone formation; large, heavy animals have been known to fall in the fields and have been unable to stand until a balance of minerals was provided by the diet. Certain excesses of minerals in water, such as fluorine or molybdenum, can cause a displacement of vital trace elements. Muir [23] described a syndrome of depigmentation, diarrhea, and emaciation in cattle which grazed on pastures which contained excessive amounts of molybdenum. The disease was cured by the administration of copper sulfate. The amelioration of symptoms in many cases of polymorphic light eruptions by the intravenous use of gold sodium thiosulfate may be predicated on the theory that gold is being substituted for other trace elements (such as copper, manganese, boron, fluorine, zinc, molybdenum, and cobalt) in essential enzymal reactions in the cellular metabolism of the body. Little is known about the effects of abnormal amounts of these trace elements in the diet and drinking water on light sensitivity. The great preponderance of light-sensitive eruptions in western Oklahoma, western Texas, and southern Colorado, where the fluoride content of the drinking water in many localities is much higher than that recommended by health authorities, suggests further investigation.

Alterations in ground substance and connective tissues of the last two patients was demonstrated on microscopic examination. Degenerated connective tissue and masses of colloid, with fragmentation of collagen fibers, were evident. Brunsting and Mason [4] stated that in chronic porphyria, milia occur in the areas of skin that have been affected by light. In discussing colloid pseudomilium, Arnold [3] reported hard, sharply elevated, round and oval, flat-topped papules on the backs of the hands of a man constantly employed outdoors. Pathological studies showed degenerated

21. Miller, J. J.: Enzymes and Their Relation to Disease, read before the American Academy of General Practice, Salt Lake City, Sept. 7, 1950.

22. Lerner, A. B., and Fitzpatrick, T. B.: Biochemistry of Melanin Formation, Physiol. Rev. **30**:91, 1950.

23. Muir, W. R.: The Teart (Molybdenum-Bearing) Pastures of Somerset, Vet. J. **97**:387, 1941.

connective tissue and ill-defined masses of colloid, with fragmentation of collagen fibers. In both the description of the lesions of the hands and the pathology this case parallels Cases 2 and 3.

Vitamin C is intimately associated with the synthesis and maintenance of collagen, the chief protein of all connective tissue and particularly that of the skin. It therefore must be mentioned in discussing degenerative changes in collagen. Ascorbic acid may have a role in protein degradation. It has been observed to deaminize and decarboxilize a series of amino acids and to promote the conversion of tyrosine to dihydroxyphenylalanine in the presence of ultraviolet rays. Hailey [24] Hitch,[25] and Way [26] have stressed the vital role of vitamin C in the treatment of colloid milium.

Way's patient went without fresh vegetables and fruits for months at a time. Urine studies revealed a marked decrease of ascorbic acid excretion. This patient was given foods high in ascorbic acid, and 10 months later there was complete absence of the milia of the forehead.

It may well be that steroid-induced mineral- and vitamin-deficiency alterations in the connective tissue and its elements may alter the cutaneous response to sunlight and the resultant lesion be determined by the nature and degree of the physiological alteration, which is detected in the morphological changes seen histologically.

While a multiplicity of factors have been related to light sensitivity, including certain vitamin deficiencies, most of these factors impinge upon the hormonal equation and influence the endocrine status of the patient. Intense or prolonged light alone has been shown to influence markedly the pituitary-gonadal axis, and, although there are no data upon human subjects, there is ample experimental proof from laboratory animals that light is a powerful stimulant to pituitary production of gonadotropins.

SUMMARY

The three cases reported are of great interest, since they illustrate extreme forms of light-sensitive eruptions. While the endocrine aspects were not clearly defined in two, the findings are suggestive. It is felt that in similar cases abnormal liver function should be ruled out, especially if any abnormal endocrine findings are detected.

ABSTRACT OF DISCUSSION

Dr. Arthur R. Woodburne, Denver: Solar dermatitis was first classified and extensively investigated by Sir Jonathan Hutchinson. His original observations appeared in a compilation of his clinical lectures published in a book entitled "Lectures on Clinical Surgery on Certain Rare Diseases of the Skin." He was the first to emphasize the polymorphic character of light sensitivity. In this and subsequent publications he presented many cases with various degrees of skin damage produced by light sensitivity, and in one discussion he related some of the serious forms to Kaposi's disease (*Tr. Clin. Soc. London* **22**:80, 1889). In this discussion he reported two cases of verrucous changes similar to those in Cases *2* and *3* presented here.

H. Radcliffe Crocker, in a discussion of "Winter and Summer Recurring Eruptions" (*Brit. J. Dermat.* **129**:39 [Feb.] 1900), reported one case of recurrent summer eruption with hypertrophic papules of the wrists and dorsal surfaces of the hands closely resembling lichen planus, and in his closing paragraph he said of such eruptions, "In both groups are odd unclassifiable cases." Thus he also emphasized the polymorphic character of these eruptions.

24. Hailey, H.: Colloid Milium, Arch. Dermat. & Syph. **58**:675, 1948.

25. Hitch, T. S.: The Sun and the Skin, North Carolina M. J. **10**:299, 1949.

26. Way, S. C.: Colloid Milium: A Vitamin Deficiency Disease? Arch. Dermat. & Syph. **45**:1148, 1942.

It is interesting to have reemphasized the rather unusual forms of solar dermatitis. Drs. Lamb, Morgan, and Shackelford have done much to stimulate our interest and, with their studies in 17-ketosteroid chemistry and special stains to reveal alterations in ground substance, have added much to our knowledge of the chemical alterations as a background of these conditions.

They have suggested many problems regarding trace minerals and vitamins in relation to light sensitivity and the reaction of the skin to light irritation. Their theory that a high fluoride intake replaces cobalt, copper, and other minerals necessary in some enzyme and vitamin interreactions to prevent solar dermatitis is especially interesting to me. Since reading their paper I have tried to coordinate fluoride in water supply with solar dermatitis without any very definite conclusions. On the western slope of the Rocky Mountains fluoride is absent from the water of most communities, and yet as much solar dermatitis is seen there as in the eastern part of the state. The water of the Denver area and most deep-well water has 0.7 to 1.2 parts per million of fluorine, which is optimal. I know of no large area near Denver where the fluoride content of the water is extremely high, and yet the incidence of solar dermatitis is probably as high there as it is anywhere on this continent.

Dr. Louis Brunsting at the last meeting of the American Dermatological Association made the statement that disturbances in porphyrin metabolism were practically never the cause of photosensitive reactions, an observation illustrated here by the fact that Patients 1 and 2 showed no abnormal porphyrin metabolism.

The problems raised here of the interrelation of 17-ketosteroids, vitamins, and trace minerals will require prolonged study, and I am sure that I am not qualified to discuss them here, and yet, through continued clinical investigation, we have been able to apply some of the knowledge derived to the benefit of the patient.

Many patients suffer from solar dermatoses, and in our part of the country these can be incapacitating. Consider the problem of a rancher with a skin sensitivity to light in a country where bright sunshine is usual 360 days of the year and 90% of his work must be done out of doors.

The problem of treatment is not simple. Some patients will respond to androgenic therapy as outlined in the article under discussion; however, many patients will not, and it will tax the therapeutic resourcefulness of the most experienced practitioner to make it possible for these people to remain on their farms and ranches. Some patients will respond to gold therapy in the form of gold sodium thiosulfate given intravenously or one of the colloidal gold salts given intramuscularly. Such patients respond to relatively small doses—10, 20, or 30 mg. a week for a few weeks often producing a remarkable improvement. Sodium paraaminobenzoate given by mouth in doses of 0.5 to 1.0 gm. four times a day has helped many patients. Large doses of vitamin B complex have been helpful in a few cases.

These four methods have been the effective types of internal medication in my experience. The effectiveness of adjuvant protective therapy must be stressed. There are many sun-screening preparations on the market. The old preparation of 10% phenyl salicylate in a suitable base is still effective. However, several newer preparations have also proved adequate. Kesten will soon publish the results of investigation of the protective efficiency of many commercial and national-formulary preparations. She has shown that ordinary carbolated petrolatum is as effective as any; however, there are many more cosmetically acceptable preparations, particularly those containing salts of paraaminobenzoic acid, such as Skolex, and those containing methyl anthralinate, such as A-Fil, which are commercially available and very effective.

We should, therefore, combine the usual means of attack that we employ in treating any other externally caused dermatosis; namely, (1) avoidance of exposure, (2) protection, and (3) systemic medication to raise resistance and help correct the underlying chemical fault.

NONPIGMENTED MALIGNANT MELANOMA D'EMBLÉE

Report of a Case

HUGO HECHT, M.D.
CLEVELAND

THE FOLLOWING case is perhaps the first to be reported of nonpigmented malignant melanoma *d'emblée*.

A 55-year-old white man was first seen by me on Jan. 22, 1951. He was sent to me because of a little tumor at the left side of the nose near the saddle; his family physician regarded it as a mole. Both the patient and the family physician were sure that the skin was normal before the lesion appeared. It was a round, firm, yellowish tumor 7 mm. in diameter and 1 mm. high. There was no pigmentation. The tumor was limited to the skin and was freely movable. The regional lymph glands were of normal size.

The little tumor was excised under local procaine anesthesia and the bleeding base thoroughly cauterized. It healed with a fine scar.

There were no signs or symptoms of a tumor in other parts of the body. The microscopic diagnosis (Figs. 1 and 2) was not clear. I regarded the tumor as malignant, and suggested to the patient a complete clinical check-up, especially of the gastrointestinal tract and kidneys. The patient refused and went on working. However, five months later while shaving he noticed a little lump under the left jaw. He again delayed a visit to his physician, whom he did not see until the lump became larger and painful. A dentist found nothing wrong with his teeth, and an x-ray examination gave normal results. His local physician performed an aspiration (no microscopic examination was made), after which the mass gradually decreased in size and the pain gradually disappeared.

The patient entered the hospital on July 31 with a very hard mass (3 by 4 cm.) in the inferior region of the mandible on the left side; it was slightly movable and tender. The axillary nodes were moderately enlarged and freely movable, but not tender.

A specimen taken on Oct. 8 was on section pinkish-white and soft, with numerous areas of friable yellow fragments. The microscopic diagnosis (Fig. 3) was secondary carcinoma of a lymph node (hypernephroid type).

A gastrointestinal series revealed no evidence of organic lesions in the upper gastrointestinal tract or in the colon. Cystoscopy and a retrograde pyelogram showed nothing abnormal. A short time later the patient went to another hospital. In view of his previous history, cystoscopy was carried out. This showed no kidney abnormality.

On Aug. 29 a biopsy was done of the neck mass and the lesion reported as metastatic cancer. In view of the obscure origin of this tumor, a radical neck dissection was carried out on Sept. 7. On Oct. 4, a small thrombosed vein was removed from the right calf. On Nov. 29 a 1-cm. subcutaneous nodule was noted on the right chest. This was watched for a short period and removed on Jan. 8, 1952, along with a second nodule of recent origin in the abdominal wall (Fig. 4). Both nodules showed metastatic carcinoma. At that time repeated cystoscopy and pyelograms were negative. Shortly thereafter severe pain developed over the left fibula, and in addition new tumors appeared in the left axilla, over the scapula, and over the sacrum. At this time, additional nodules of the left chest wall and abdominal wall were removed.

From approximately early February, increasing evidence of metastasis within the abdomen developed, with low-grade obstruction, diarrhea, and vomiting. In March a diagnosis was made of partial colon obstruction, but it was considered advisable to carry on with a low-residue diet, without further surgery. He was discharged from the hospital for the last time on March 29.

During the course of his last hospital admission, x-ray examination of the chest, which had previously been negative, showed metastatic carcinoma of both lungs. He died at his home in the first week of June, 1952. A postmortem examination was not permitted; it was therefore impossible to establish a definite diagnosis as to the primary site. The surgeons had the impression that the tumor was of renal origin.

Histopathology.—A slide was prepared which showed the skin tumor removed Jan. 22, 1951. A microscopic description by Dr. B. S. Kline and Dr. A. Hochwald was as follows: Three sections showed an area about 7 by 3 mm. composed of nests of large vacuolated mononuclear cells separated from each other by irregular bands of large connective-tissue cells. There were scattered mitotic figures in the vacuolated cells, which had nuclei varying in size. Some nuclei were very large and hyperchromatic, with prominent nucleoli. In places the picture suggested transformation of large connective-tissue cells into rounded cells. Suggested diagnoses were (1) sessile fibroxanthoma, (2) liposarcoma, (3) metastatic renal cancer, (4) sebaceous-gland neoplasm, (5) leprous granuloma, and (6) ganglioneuroma.

This slide was shown to a group of pathologists, who differed greatly. One of them (Dr. H. Lund) suggested clear-cell carcinoma, with the following alternatives: 1. Primary skin

Fig. 1.—Low-power view showing circumscribed tumor intimately associated with epithelium. Hematoxylin and eosin; × 6.25.

cancer; this occurs but is usually only locally aggressive. 2. Metastatic lesion to skin from the kidney; this cannot be excluded. 3. Mesenchymal tumor; rhabdomyosarcoma.

Because of the divergence of opinions the slide was sent to three other pathologists, who gave the following answers:

Dr. H. Montgomery, Mayo Clinic: "The section is a very difficult one to diagnose, and I doubt that you will obtain any uniformity of opinion. My first impression was that of hemangioendothelioma because of the vascularity and apparent origin from some endothelial cells of the smaller vessels. I also thought of myxosarcoma. I do not believe this is a benign lesion.

Dr. J. R. McDonald, Rochester, Minn.: "Because of one or two small areas of apparent origin from the epidermis this may be an unusual type of squamous-cell epithelioma, Grade 4, or else a melanoepithelioma. I remain to be convinced of the diagnosis of squamous-cell epithelioma but think melanoepithelioma without pigment is a good possibility.

"The lesion does not look like a metastatic malignancy to me, and I am quite sure it is not a sebaceous-gland neoplasm. I would rule out leprosy and certainly ganglioneuroma of the skin. Stains for mucin if positive might suggest a metastatic lesion from the gastrointestinal tract. I have seen several cases of hemangioendothelioma in which myxomatous change took place, but I would still be inclined to favor this diagnosis."

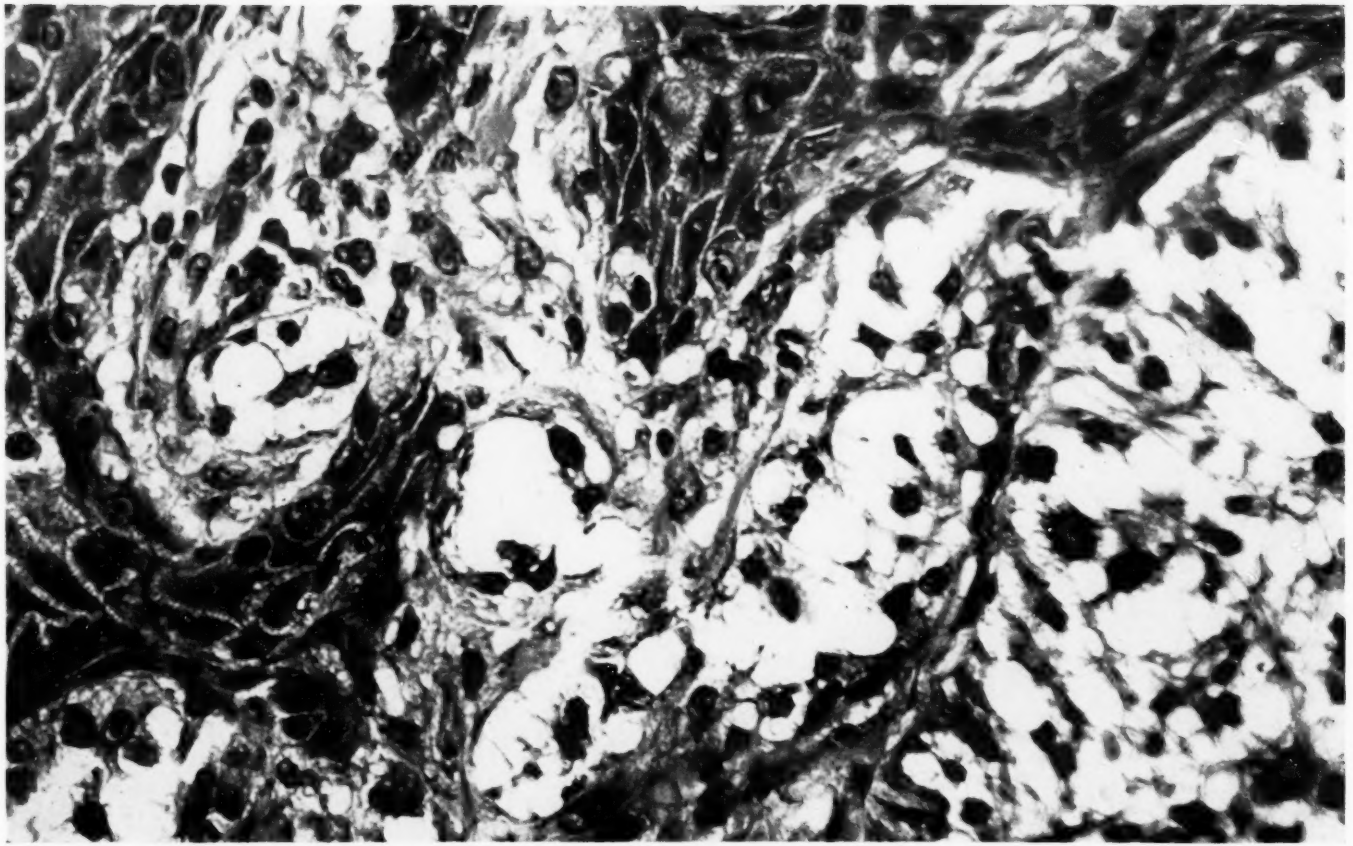

Fig. 2.—Gradual transition from epithelium to tumor. Hematoxylin and eosin; × 250.

Dr. Paul Klemperer, New York: "I believe that the slide disclosed a nonpigmented malignant melanoma. You might want my reason for this diagnosis. I feel that the combination of epithelial-like cells and spindle cells in the same slide is seen most often in such tumors. I may add that whenever I see a tumor which does not fit the conventional diagnosis of carcinoma or sarcoma I think of melanoma."

Dr. Hermann Pinkus, Monroe, Mich.: "I think the lesion is a malignant tumor. Beyond that I am much less certain. In studying the sections of the small superficial tumor, I was impressed

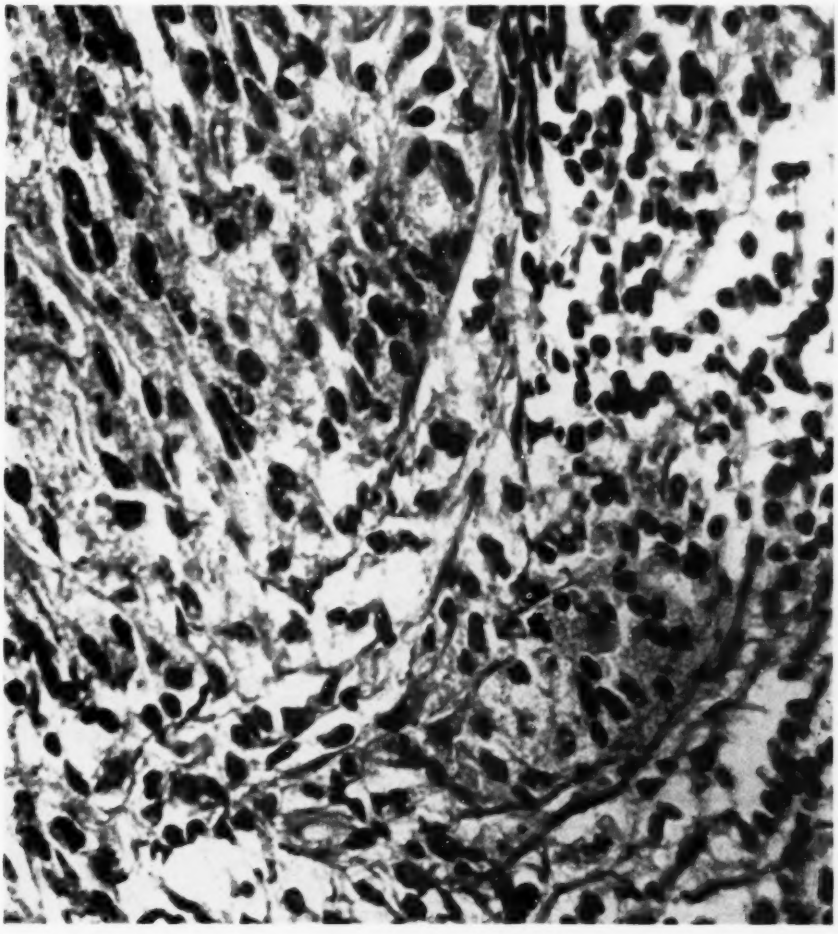

Fig. 3.—Lymph node showing secondary malignancy. Hematoxylin and eosin; × 250.

by the fact that as one approaches the tumor from both sides there are many large cells at the epidermal junction which form nests and have all the characteristics of junctional nevus cells. These parts also show an inflammatory reaction in the corium.

"The tumor cells themselves appear to have very fragile cytoplasm. One section on the slide even shows considerably more shrinkage than the other. The great variability of size, the presence of multinucleated tumor cells, and the close association of tumor cells with epidermis all seem to favor a diagnosis of malignant melanoma. Of course, I did not see any pigment, and

I also did not find the vacuolization of the nuclei which sometimes is helpful in supporting a diagnosis of melanoma. I wonder whether a plain silver stain might bring out some (pre) melanin granules. I have seen instances in which melanotic melanoblasts with similar large, finely vacuolated cell bodies gave a diffuse dopa reaction and also contained some silver-stainable granules.

"Another possibility which occurred to me is that this may be hemangiopericytoma, but I have practically no experience with this type of tumor and just want to mention it is as a

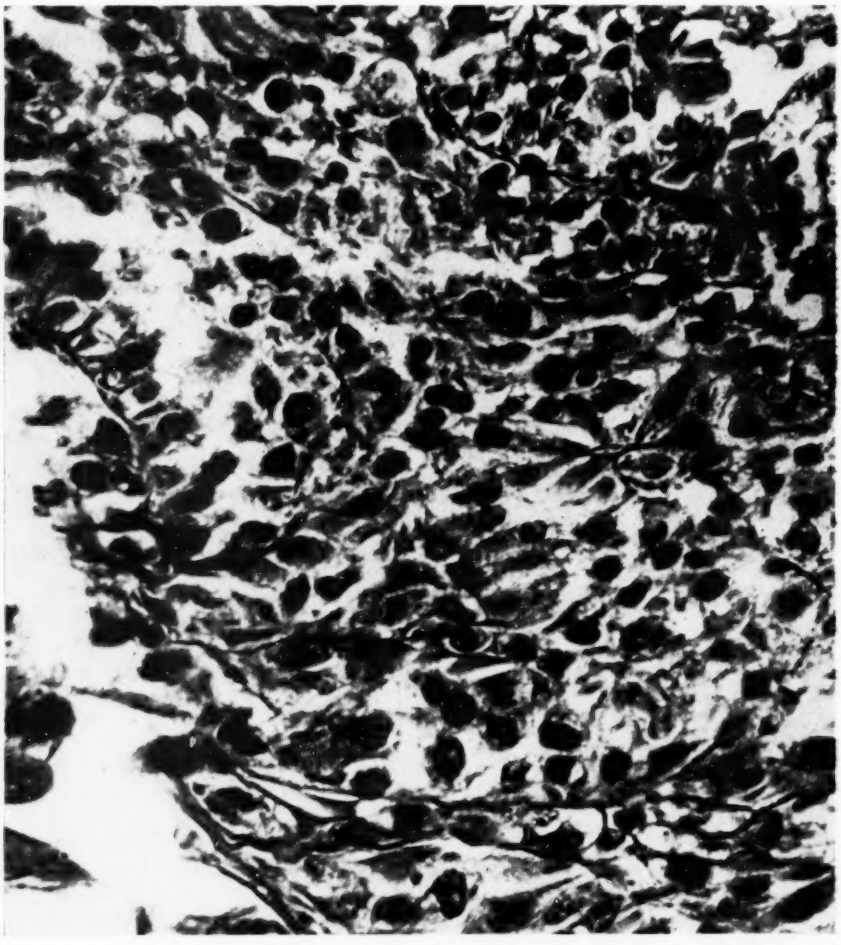

Fig. 4.—Secondary tumor in subcutaneous tissue of abdominal wall. Hematoxylin and eosin; × 250.

suggestion. The peculiar arrangement around blood vessels, with the tumor cells on the basement membrane, gave me the idea. It might be that a silver reticulum stain would better elucidate the structure of the tumor and would help you to arrive at a definite diagnosis."

Another slide was prepared from the submaxillary gland removed in August, 1951. Sections of the nodular structure showed a lymph node infiltrated by malignant neoplastic cells; many were large and rounded, with clear cytoplasm and small nuclei. The tissue was alveolated by scant stroma. Elsewhere the neoplastic cells were polygonal or spindle-shaped, in compact

bundles In places they adjoined one another for a distance of several millimeters. Some cells had two nucleoli, and there were scattered mitotic figures. There was an area of necrosis several millimeters in diameter. An outer wall of dense collagenous connective tissue formed the capsule. The final diagnosis was secondary carcinoma of a lymph node, hypernephroid type.

A suggestion was made to investigate the kidneys, adrenals, skin, thyroid, testes, and salivary glands. A gastrointestinal series revealed no evidence of organic lesion in the upper gastrointestinal tract or in the colon, and a retrograde pyelogram was normal.

A third slide was made from a tumor in the chest wall removed Jan. 29, 1952. It showed the same picture as the second slide. One of the pathologists who examined the slide (Dr. B. S. Kline) pointed out the similarity of the elongated cells seen in the tumor to nerve fibers in muscle spindles which form the hypolemmal net. Bremer [1] gives the following description:

"The spindles are slender bundles of poorly-developed fibers. Around these muscle cells, nerve fibers wind spirally. All the muscle spindles are formed during embryonic life. They have not been found in all muscles, and in certain muscles they are regularly more numerous than in others. They are numerous in the distal muscles of the limbs, and in certain muscles of the neck."

This slide could not help in determining the origin of the tumor cells.

COMMENT

This is a very interesting but also puzzling case. The main problem to be discussed is whether the first skin lesion was a primary tumor or a metastasis in the skin originated by a tumor hidden somewhere in the body.

The pathologists suspected a secondary tumor. The dermatologists preferred the diagnosis of a primary lesion. Because an autopsy was impossible, there is no definite proof for one of these alternatives. I think it was a primary lesion because (1) during one year of repeated x-ray and urological studies there was never any sign of a tumor of the kidneys, as the surgeons suspected, or of a tumor elsewhere in the body, and (2) after the original tumor was removed, the patient had four months of perfect health before the first metastasis made its appearance. This metastasis was located in a lymph node in the vicinity of and on the same side as the first skin tumor. The second metastasis was farther down but still on the same side. Only after the second metastatic tumor was removed did the malignancy spread out to other regions of the body, and there were still no symptoms of an internal primary tumor. I conclude, therefore, that there is a strong probability that the little tumor at the forehead was the primary lesion.

The second problem is that for 55 years there was nothing at the spot where the little tumor arose out of normal skin. There were no moles, freckles, or more pigmentation than that of the surrounding skin. Reverting to Cohnheim's theory of "cell rests" has for the pathologist of the present time only historical interest, because there is no evidence of the existence of embryonic "cell rests." There is, however, clear evidence that tumors arise from fully differentiated adult cells (R. A. Willis). It could be that some embryonic kidney cells were dormant at the site of the first lesion. Only after the patient reached the cancer stage did these few cells start to grow. What carcinogen caused them to start growing and multiplying cannot even be guessed. It must be remembered that several pathologists and surgeons saw some similarity to renal tissue. How could renal cells be present in the skin of the forehead if not from the fetal tissue, when no evidence of a primary renal tumor could be found?

1. Bremer, J. L.: A Text-Book of Histology, Philadelphia, The Blakiston Company, 1936, pp. 136-137.

If one discards the theory of a renal origin and turns to the assumption that the tumor was a primary one and a nonpigmented melanoma, one has to realize that melanomas are not too common. They are rare in children. Most of them grow from preexisting moles or even freckles, as in the case published by Pautrier and Woringer,[2] in which a malignant melanoma developed from a simple freckle.

In the present case there was only normal skin present at the site of the lesion before the little tumor developed. It is known that in certain cases a melanoma can arise in normal skin without a previous lesion (*mélanome d'emblée* of Dubreuilh). It is probable that a congenital malformation with inclusion of embryonal blastomes is the basis of a tumor which develops after many years of dormancy. What causes this sudden animation is a matter of speculation, as has been mentioned. Trauma, in the form of friction, scratching, or pressure, or senescence of the surrounding tissue, with lowering of the normal resistance so that the quiescent embryonal cells start to multiply, may be the agent, but no one knows.

A frequent cause is injury to a mole. But, subungual melanomas occur without preexisting moles. Malignant melanomas arise from existing pigmented or nonpigmented nevi, from precancerous melanosis, or from microscopically normal skin (*mélanome d'emblée* of Dubreuilh).

Trauma as a cause was suggested by Herzberg,[3] whose patient had a highly polymorphic-cell tumor, composed of fairly large, spherical-polyhedrical cells which contained iron-free pigment. In the cutis were large clusters of plasma cells. This patient had had a pigmented nevus at the left side of the chest since birth; from the lower part of it a tumor developed, caused apparently by permanent friction of the suspenders during work. Herzberg's diagnosis was melanoblastoma with little pigmentation.

Ramel [4] called attention to the observation that pediculated melanomas are achromatic.

A nonpigmented malignant melanoma in a 21-year-old woman was reported by G. C. Andrews.[5] A mole had developed on the right cheek three or four months before.

ORIGIN OF THE TUMOR CELLS

Melanoma cells come from the epidermis. They can be round, fusiform, or pleomorphic. They can be pigmented or unpigmented. All these cell forms can be observed in one tumor, as in the present case. Klemperer remarked in his letter that the combination of epithelial-like cells and spindle cells in the same slide is usually seen in malignant melanomas.

There are two theories: An epithelial origin has been suggested by Unna and supported by Bloch, Darier, Miescher, and others. All these are dermatologists. However, pathologists also favor the epithelial origin (R. A. Willis). A nervous

2. Pautrier, L. M., and Woringer, F.: Mélanome de la région frontale, Bull. Soc. franç. dermat. et syph. **40**:159, 1933.

3. Herzberg, T. T.: Unusual Malignant Tumors of the Skin, Dermat. Wchnschr. **120**:729, 1949.

4. Ramel, E.: Du Mélanome pédiculé à prédominance achromique, Bull. Soc. franç. dermat. et syph. **36**:161, 1929.

5. Andrews, G. C.: Malignant Melanoma, Arch. Dermat. & Syph. **62**:461 (Sept.) 1950.

origin is favored by Masson, Audry, and Ewing. It should be mentioned that the pigmented dendritic cells of the epidermis are sometimes cited as the exclusive source of melanomas.

A. C. Allen [6] made an important contribution in this field. He stated that cutaneous malignant melanomas arise from junctional nevi. Therefore, malignant melanomas are epidermogenic, and they should be classified as carcinomas for this reason rather than because of so-called neuroectodermal derivation. The evidence contradicts the impression that malignant melanomas arise from the common mole. He stated that it is possible to differentiate a primary from a metastatic melanoma, because metastatic melanomas do not provoke the junctional change.

In the case discussed, Pincus stated that there were many large cells at the epidermal junction, which also formed nests and had all the characteristics of junctional-nevus cells. In a recent paper Garfinkle and Cahan [7] concluded that the presence of a junctional change in the mucosa of the esophagus immediately adjacent to a melanocarcinoma proved that the esophagus was the primary site. These parts also show inflammatory reaction in the corium.

Allen called attention to the observation that metastatic lesions never show any inflammatory infiltration. This is one more reason why I regard the described lesion as a primary tumor. In regard to the absence of melanotic pigment, it should be remembered that pigment is not necessary for development of a melanoma; though it is characteristic (Deelman,[8] Horwitz [9]). However, metastases of typical melanodermas are frequently nonmelanotic.

CONCLUSIONS

A case is presented of a small skin tumor which caused difficulties with regard to diagnosis, the question of malignancy, and the origin. A follow-up of one and a half years helped to establish its malignancy.

Rapid spreading to an early end favored the diagnosis of a tumor of great malignancy, such as melanoma.

The mixture of different cells in the little (primary?) tumor made a diagnosis of a nonpigmented melanoma probable.

Because it developed out of seemingly normal skin, it was thought to belong in the group called malignant melanoma *d'emblée* by Dubreuilh.

This would be the first case published as nonpigmented malignant melanoma *d'emblée*.

821 Schofield Building, Cleveland (15).

6. Allen, A. C.: A Reorientation on the Histogenesis and Clinical Significance of Cutaneous Nevi and Melanomas, Cancer **2**:28, 1949.

7. Garfinkle, J. M., and Cahan, W. G.: Primary Melanocarcinoma of the Esophagus: First Histologically Proved Case, Cancer **5**:921, 1952.

8. Deelman, H. T.: Nevus Tumors Without Pigment, Acta dermat. venereol., 1922.

9. Horwitz, A.: Melanotic Tumors, Non-Melanotic Melano-Epitheliomas and Their Relation to the Melano-Epitheliomas, Ann. Surg. **87**:917, 1928.

DERMATITIS VENENATA DUE TO NATIVE WOODS

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CHICAGO

DERMATITIS venenata in its relation to the plant world comprises more than is fully appreciated unless one especially studies the subject. The plant world consists of weeds,[1] flowers, vegetables, fruits, and trees. All trees have a potential irritant in the bark, freshly cut wood, dried wood, sawdust, leaves,[2] or other parts. Most of the recent literature on dermatoses due to woods [3] emphasizes the importance of exotic or foreign woods, with less mention of native woods as a cause of allergic dermatitis.

Recently a wood worker was disabled seven months with a generalized dermatitis venenata simulating lymphoblastoma. His trouble throughout was attributed to sawdust, but the usual tests and investigations failed to establish this causal relationship. He recovered, but resuming work with sawdust reproduced the dermatosis. This recurrence as well as the results of tests confirmed the etiologic diagnosis of dermatitis venenata due to sawdust derived from native wood.

This case, with some unusual features of dermatitis venenata due to native woods, is worth reporting, since a similar one is not mentioned in the literature.

MECHANICAL TRAUMA

Seldom is the importance of mechanical trauma as a cause of dermatitis in wood workers mentioned. Sawdust and fragments of wood produced by machine tools are often sharp, this quality depending in part on the state and kind of wood. The sharp-edged particles strike the skin with sufficient force, at times, to traumatize it. Usually the reaction is transitory and superficial. In a few persons the local inflammation or traumatic dermatitis, is more serious. It may progress until there is considerable thickening of the skin and then disappear gradually if all trauma is discontinued. Also, regardless of the source, the effect of repeated mild trauma of the skin varies according to individual predisposition.

From the Department of Dermatology, University of Illinois College of Medicine, Dr. F. E. Senear, Chairman.

Read at the Seventy-Second Annual Meeting of the American Dermatological Association, Inc., Colorado Springs, Colo., April 23, 1952.

1. Shelmire, B.: Contact Dermatitis from Weeds: Patch Testing with Their Oleoresins, J. A. M. A. **113**:1085, 1939.

2. Genner, V., and Bonnevie, P.: Eczematous Eruptions Produced By Leaves of Trees and Bushes, Arch. Dermat. & Syph. **37**:583, 1938.

3. Senear, F. E.: Dermatitis Due To Woods, J. A. M. A. **101**:1527, 1933. Record, S., Jr., and Hess, R. W.: Timbers of The New World, Yale University Press, 1949.

Occasionally a mechanical or traumatic dermatitis is the forerunner of sensitization dermatitis. Defects of the skin facilitate the transition. The control of sensitization dermatitis depends in part on maintenance of an intact cutaneous surface.

The objective signs of traumatic dermatitis and of allergic dermatitis are similar. The results of patch tests are employed by some dermatologists to distinguish between the two diseases. If the worker is told of the traumatic factor he becomes more careful, and his trouble will usually improve or clear while he is working.

ALLERGIC DERMATITIS (DERMATITIS VENENATA)

Infrequently dermatitis venenata is induced through external contact with sawdust of native woods after varying periods. When sensitization occurs the early stage of the clinical picture is that of redness and scaling. Vesiculation and swelling of the hands, forearms, and face appear as the attack becomes more severe. Sometimes persons with mild attacks continue to work until vesiculation and swelling of the right hand and right forearm begin. A few become concerned only when there is involvement of the skin of the face and genitals. Then they seek medical help. Most of the attacks are due to a moderate sensitivity of the skin of the affected worker or to a daily massive exposure of a moderately sensitized person to sawdust derived from native woods of low-sensitizing capacity. If the atttack is acute the worker is disabled from three to four weeks; thus contact with the offending sawdust is discontinued. If he returns to the same work and is exposed to sawdust another attack follows within a few hours or a day. There is always a possibility that he may become desensitized, but desensitization is uncommon in my experience. Generalized attacks due to native woods seldom occur.

Itching begins early and is always an outstanding symptom in allergic dermatitis due to sawdust. Often it appears to be out of proportion to the objective symptoms.

The acute attack generally responds to treatment and subsides in three to five weeks provided contact with sawdust and with objects likely to be contaminated with it is discontinued. Dermatitis venenata due to sawdust seldom passes into unusual forms of dermatoses which may last indefinitely.

My interest is in cabinet workers and furniture makers who are exposed to the heartwood, or central portion of the trunk, which is devoid of bark. Sawdust derived from the heartwood contains one or more substances which have the capacity to cause eczema in some persons who are exposed to it. The causation is usually proved by the reactions elicited in patch tests with dry and wet sawdust. Better proof is established if improvement occurs in sensitized persons upon avoidance of the irritating sawdust, as in my series of cases.

Not the major components of wood, such as cellulose and lignin, but the minor ones, which amount to 3.3%, are of interest to the dermatologist. Some of these are resins, terpenes, and oils. Others are phenols, tannins, coloring matter, and nitrogen-containing substances. Other wood components of importance may contain the acetyl group and formic acid.

The native woods which are cutaneous sensitizers are acacia, alder, ash, beech, birch, chestnut, cedar, creosote bush,[4] elm, maple, mesquite,[5] oak, pine, poplar,

4. Smith, L. M.: Dermatitis Caused by Creosote Bush, J. Allergy **8**:187-188, 1937.

5. Fox, E. C.: Mesquite Wood Dermatitis, Arch. Dermat. & Syph. **44**:1098, 1941.

prune, and spruce. Poplar has most frequently produced allergic reactions in my practice. This fact is probably due to the presence in the wood of certain species of a glucoside which may also produce a toxic effect.

It has been known that age of onset of allergic dermatitis is variable but that the condition is more common in adults. In my series of cases of dermatitis venenata due to native woods the age at onset was from 40 to 60 years.

There was one exception in the case of a man of 21 with dermatitis venenata due to creosote bush. He was exposed to the wood for two weeks before he became sensitized. No special skill was required in his work of cooking and evaporating a woody substance into a fine powder. His fellow employees informed him that his particular work had become hazardous because it involved working with a new product which had recently arrived from Texas. I learned from several employees that powder was the wood of the creosote bush. The processed powder was used for the preparation of an antioxidant for lard known as noxdihydroguiaretic acid, commercially known as "NDGA."

Generally, the period of refractoriness to sensitization with sawdust was maintained for years and then suddenly disappeared. It was difficult to state whether or not this situation was due in part to the native woods being poor sensitizers, to individual predisposition, or to both. In some of my cases there were various factors which determined the age at onset of allergic dermatitis in workers handling native woods.

In several cases the resistance of the skin was overcome after daily massive exposure to sawdust. Once the person was sensitized, the reaction time of the second or recurrent attacks was one or two days.

Allergic dermatitis has occurred after an interval of forced interruption of work in which sensitizing factors were known to exist. In several wood workers injury or other causes resulted in absenteeism from work for varying periods were followed by attacks after resumption of work. Tommasi [6] stated that workers who returned to labor in the woods after a long absence are apt to have dermatitis for the first time. He did not mention whether the sensitization is due to leaves, bark, or sawdust.

One worker became sensitized to cocobolo wood first and to native woods later. He had worked with cocobolo wood for many years without difficulty. In his case the wood came from a new source about two weeks before the onset of his trouble.

Only a few persons were found to be sensitive to sawdust derived from native woods. It has been my experience that 1% of workers become sensitized to sawdust derived from native woods after working with it many years. My investigations showed that in some cases in new employees the condition was treated by the plant nurse or the industrial physician, a fact which may account for the small number of cases that appeared in my practice.

Woodworkers sensitized to sawdust of native woods remained skin-sensitive for years without further exposure to the allergen. Two patients were skin-sensitive two years after the original sensitization. Other patients were known to have been exposed to sawdust in their work years later, with a recurrence of dermatitis vene-

6. Tommasi, L.: Dermite dei boscaiuol: da ipersensibilità, Gior. ital. dermat. e sif. **70**:1223, 1929.

nata within a day. In all the patients available for follow-up study the persistence of sensitivity had continued despite the avoidance of sawdust.

Another interesting point in this study was the number of patients who became sensitized to more than one wood. Several workers became sensitized to a foreign wood and later to a native one. Others became sensitized first to a native wood and later to a foreign one. One patient became sensitized to four woods, all native. He was forced to give up the sawing of wood, but he was able to handle the finished wood without trouble. There were other patients with polyvalent sensitization who had no irritation from the handling of finished native woods. So far, no case has come to my attention in which the handling of finished woods of native origin has caused trouble.

There was a decided difference between the reactions of the patch tests with dry and with moist sawdust. I doubt now that the allergic character of dermatitis

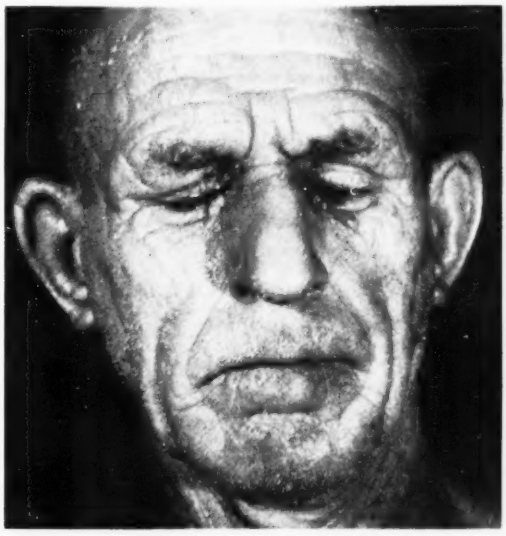

Fig. 1.—Dermatitis venenata due to poplar sawdust.

venenata was always confirmed by appropriate cutaneous tests in my series of cases. Certainly covering with moist sawdust is not an accurate or fair test, because formic acid is formed by addition of water to some woods. The worker is exposed to dry sawdust for eight hours a day, provided there is no shirking of duty. A patch test in which dry sawdust is applied on the same site for eight hours a day for three successive days more nearly reproduces the work exposure. If the worker is sensitized, such a test may be expected to reproduce his dermatitis venenata.

REPORT OF A CASE

C. J., aged 59, examined on Feb. 16, 1951, attributed his generalized dermatosis and his loss of weight to woodworking. Exposure to several sawdusts, amelioration of his eruption after cessation of work for two weeks, and exacerbation of his trouble following contact with sawdust made the diagnosis of dermatitis venenata (industrial) acceptable to me. Contrary to the usual course

of this disease, improvement failed to occur during the first month of hospitalization. During the following months intense and continuous itching, chilliness without a rise of temperature, and sleeplessness became more annoying. Meanwhile other disturbances, as a rule wholly absent in dermatitis venenata, were loss of weight (24 lb., or 11 kg.), enormous enlargement of the superficial lymph nodes, and alopecia of the scalp and axillae. Reactions to patch tests with moist sawdust derived from poplar were doubtful. Repeated histologic diagnoses of chronic dermatitis were worth while, since they ruled out cutaneous lymphoblastoma for that period. The allergic dermatitis and generalized adenopathy subsided spontaneously after six months of hospitalization. The patient recuperated in his home during the next month.

His employer on Sept. 17 purposely restricted the patient's work to sawing and sanding poplar wood. One week later the patient returned to me with generalized dermatitis venenata. When clear areas of skin were available on his back, patch tests with both old and fresh sawdust (dry) derived from poplar were done and elicited positive reactions. Both old and fresh sawdust (moist) derived from poplar produced vesicles and edema. The sawdust derived from oak and several weak oleoresins caused no reaction. The patch tests were repeated in a manner simulating the working conditions. Dry sawdust of poplar was applied to a clear site for eight hours. On the second day it was applied to the same site for eight hours, and this procedure

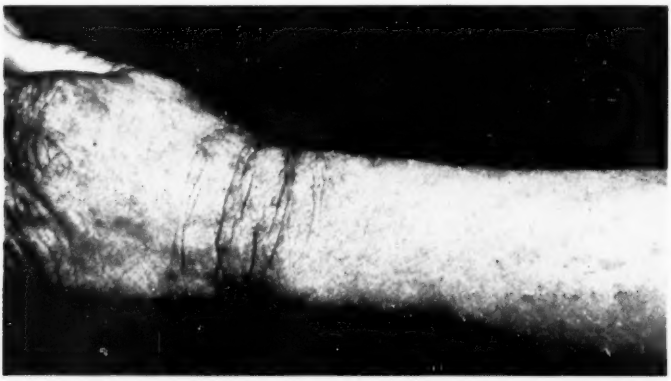

Fig. 2.—Dermatitis venenata due to poplar sawdust.

was repeated on the third day. The reaction elicited followed the same course as his dermatitis venenata.

On Oct. 20 he was sufficiently comfortable and was discharged from the hospital. At the end of another month he was well, and he later assembled plated parts in a different section of the furniture factory. He had had no recurrence at the time of writing.

The reconstruction of this patient's case was not difficult once the cause of it was found. In the beginning a subacute dermatitis of his hands and forearms was due to sawdust of poplar. Slowly his disease became generalized and intractable, so that for months it simulated cutaneous lymphoblastoma. His case then really illustrated the difficulty of distinguishing allergic dermatitis from other inflammatory dermatoses which it most closely resembled or with which it was in fact identical except in its cause. The course of his first attack of allergic dermatitis was barely characteristic, indicative, or diagnostic of the actual allergen. His second attack, following his return to woodworking, and the positive reactions of the patch tests were the two criteria which finally proved the sensitizing capacity of poplar sawdust in his case.

SUMMARY

A study showed that sawdust of native woods was the cause of either traumatic or allergic dermatitis. There was a long period of refractoriness to allergic dermatitis in the age group of 40 to 60 years. The results of patch tests with sawdust were in some patients confusing and inconclusive. Sensitization was permanent in patients available for follow-up study.

The unusual cases had the same features, and in addition: (1) several patients were sensitive to more than one wood, and one was sensitive to four native woods; (2) one patient was sensitive to processed powder of the creosote bush, which was used as an antioxidant for lard, and (3) one patient with allergic dermatitis simulating lymphoblastoma due to poplar sawdust was disabled seven months.

ABSTRACT OF DISCUSSION

Dr. Francis E. Senear, Chicago: I had a special interest in this subject some 20 years ago when I reported a case of sensitivity to wood. I have had nothing like the vast experience with dermatitis due to woods that Dr. Weber has had in his practice, in which he sees so many industrial dermatoses, and consequently I must depend largely upon the literature in dealing with this subject.

The list of native woods recognized as capable of causing dermatitis, as Dr. Weber listed them, has been considerably expanded in the last 20 years. Much more attention used to be given to eruptions due to foreign woods.

Dr. Weber did not have time, of course, to cover many points which he mentioned by implication, one of which is the variation in response to the same wood. It has been shown that the amount of allergen or, as some people think, of toxin rather than allergen, varies in the same wood from the same source and from lot to lot.

Australians have noted that the Queensland maple coming from a certain part of Australia may give rise to dermatitis, while no eruption is caused by trees from other parts.

Dr. Weber has emphasized that in the case of dermatitis due to contact with native woods, there is usually a long period before sensitization, but the period is not necessarily long. In the case I described some years ago, the patient had only a slight exposure to sawdust of the yew tree when he used glass to scrape the bows which he used in archery. His exposure was not for long at any one time, and the periods of exposure were infrequent.

Dr. Weber said that in his experience once the sensitization appeared resistance did not develop. Again, that is the common experience, but there are exceptions. It has been pointed out that with certain woods, while sensitization persists with continued exposure to other woods, a resistance does develop with continued exposure.

Dr. Weber also said that freshly cut woods usually gave rise to trouble. This observation is true in the experience of nearly every one, but, again, there are exceptions. Certain woods may stand for a long time before they cause sensitization. One of the tropical woods, known as renga wood, which has been used in furniture making, does not cause trouble until the furniture becomes old and the wood begins to disintegrate.

Dr. Weber said that patch testing with moist sawdust has its faults and recommended a procedure which more nearly approximates the working conditions of persons who are making furniture or other wood products. But it has been pointed out by practically every one who has worked in this field that a reaction often develops only when the worker is sweating or is much more intense when he is sweating. Consequently, I believe that exposure in industry would be to moist sawdust. While his suggestion is a practical one, it would probably be well to supplement dry-sawdust testing with moist-sawdust testing.

One thing I should like to ask Dr. Weber is whether he has encountered any of the systemic effects which occur occasionally with tropical woods but apparently are rarely seen in association with exposure to native woods.

Dr. Weber has commented upon mechanical injury to the skin, which is unrelated to the particular case he reported but of which, nevertheless, we do have to think in such cases. There

has been described, for example, a type of eruption due to exposure to birch bark, which has a fine powdery content on the inside that apparently plugs the follicles and gives rise to trouble in that way. There have also been described what are spoken of as "crocodile hands" from the handling of bark. Such conditions suggest a matter that Dr. Weber suggested in his paper but did not have time to stress; i. e., that the point of view is different when the worker is dealing with the whole wood, that is, with the bark stripped, and when he is handling logs as workers do in the sawmills, as wood cutters do, and so on.

Dr. Marcus R. Caro, Chicago: It is important in the case of wood workers not to limit patch tests to the woods with which they happen to be working. I have in mind particularly a patient whom I saw a number of years ago, a cabinet worker who worked with very few hard woods. Patch tests with all these woods had been performed previously with negative results. I did additional patch tests with many other woods, and I obtained a strongly positive reaction to poplar, a wood which he insisted he had never handled in his work. Further investigation showed that three floors above his place of work there was a factory in which caskets were made in which poplar was the only wood used. Apparently enough poplar sawdust floated down from the third floor to sensitize this worker and to give him serious trouble.

Dr. Leonard F. Weber, Chicago: I thank Dr. Senear and Dr. Caro for their discussion. Dr. Senear's contribution to dermatitis venenata due to woods and sawdust, in his comprehensive article in 1932, has been useful to me many times. My first experience with dermatitis due to woods was in a violin player with a folliculitis on the left side of his neck and chin. Dr. Pusey and Dr. Senear thought that ebony wood was not a factor in this case. I believed at that time we all overlooked the importance of the mechanical factor in producing his folliculitis. Later, several patients had contact dermatitis due to sawdust of poplar. Since then many native woods have been proved to be a cutaneous irritant.

Originally I had a list of about 10 or 12 woods, both foreign and native but mostly foreign, that were regarded as cutaneous irritants. Recently the list has increased, particularly in regard to native woods. My object in the present article was to call attention to the possibility of chronic lichenified dermatitis caused by an infrequent cutaneous sensitizer. Generally plants cause an acute explosive attack, as with poison ivy or primrose. In one patient a chronic lichenified dermatitis persisted six months after complete removal from sawdust. In other words, there was a sensitizing factor which continued beyond the usual time.

Dr. Senear mentioned the sweat factor and a seborrheic background as predisposing causes in wood dermatitis. In my cases these factors were always considered but were not present. The mechanical factor should be kept in mind because it may predispose to sensitization dermatitis in some cases.

Dr. Caro mentioned a case in which the possibility of dermatitis due to sawdust could have been overlooked. His case recalled an interesting private patient of mine with a contact dermatitis due to sizing material in underwear. Later this patient worked with pine wood, which caused several acute attacks of dermatitis. Since woodworking was an occasional job, or a hobby, detective work was required to solve his trouble. Most of my cases have been in industrial instead of private patients. I believe that a better understanding of the chemistry of woods would be helpful to dermatologists.

SQUAMOUS CELL CARCINOMA OF THE VULVA SECONDARY TO GRANULOMA INGUINALE

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THE CASE to be described is the first in the literature in which the development of carcinoma of the vulva secondary to granuloma inguinale is without doubt. There are in the literature, however, case reports of squamous cell carcinoma of the genitalia that developed at sites previously involved by granuloma inguinale, but none in which this sequence of events can go unquestioned with regard to the vulva itself.

REPORT OF A CASE

W. G. (No. 38–901), a 16-year-old Negro girl, was admitted to the clinic on Oct. 14, 1938, because of multiple lesions of the vulva of approximately six months' duration. The lesions were granulomatous, beefy red, and covered with a serosanguineous exudate; they involved the fourchette of the vagina, a part of the right vaginal wall, the right labium minus and labium majus, the right genitocrural fold, and in great part the right inguinal region. There were two small nodules adjacent to the anus, but no involvement of the anus was noted.

Donovan bodies were seen on Oct. 14, 1938, in the smears made from the lesions. Dark-field examination of serum from these lesions revealed no Treponema pallidum. The serological tests for syphilis (Wassermann, Kahn, and Kline) gave negative reactions. Repeated Frei tests had negative results.

The patient received eight injections of stibophen (Fuadin), 5 cc. each, intramuscularly at approximately weekly intervals until Dec. 9, 1938, at which time she was considerably improved—nearly well, clinically. After this visit, she became delinquent.

On May 4, 1939, she returned with a recurrence of all the lesions observed at the time of the original admission, but with progression and extension of these lesions. The left side of the vulva was now involved also.

Donovan bodies were demonstrated again in smears taken from the lesions. Reactions to repeated Frei tests were negative. Wassermann, Kahn, and Kline tests on May 11, 1939, gave negative results.

A biopsy specimen (Fig. 1) was taken on May 4, 1939. Microscopic examination showed areolar fibrous tissue covered by stratified squamous epithelium. This epithelium revealed fairly marked thickening and acanthosis, with the immediately underlying tissue consisting of a peculiar granulation type made up of a mixture of many cells. Numerous small blood vessels well filled with red corpuscles were also seen. The cell types were interesting and showed the following variety: First, plasma cells and lymphoid forms were very numerous. There were a small number of scattered eosinophiles and in many focal areas relatively large numbers of neutrophilic leuco-

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cytes. Scattered macrophages having relatively broad cytoplasm were fairly numerous. This cytoplasm appeared somewhat speckled or foamy but, in the hematoxylin-eosin preparation, failed to show any definite organisms.

In preparations made and stained by the Giemsa technique the fairly numerous macrophages described above contained numerous small bodies having the following appearance: The small clumped central rods which stained from purple to red were surrounded by a clear zone or capsule which outlined the body as a discoidal or oval-shaped structure with a diameter approximately one-half that of a red cell, or about 3 μ.

Some individual macrophages contained very large numbers of these bodies. Sometimes the staining of the central material was somewhat variable, presenting in part a purplish color and in part a reddish color, giving the false appearance of two bodies in one capsule. In many respects, these bodies had the appearance of encapsulated bacilli or encapsulated diplobacilli. The

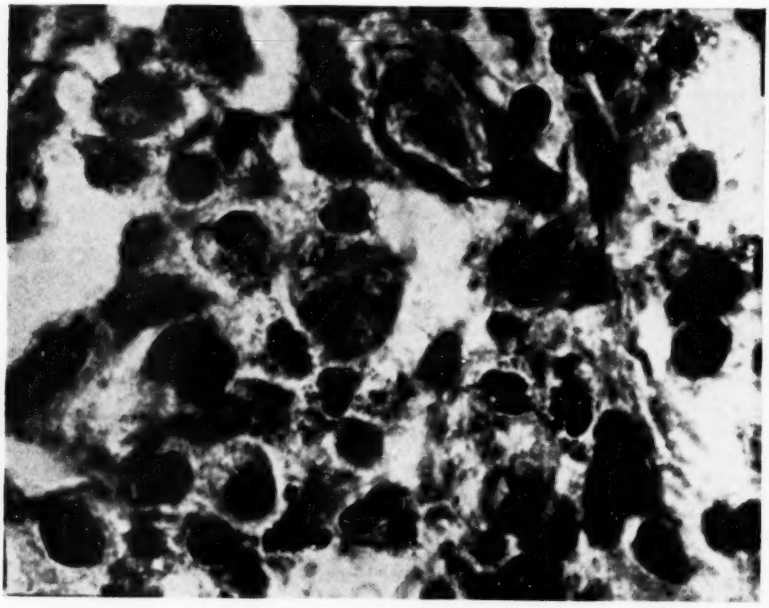

Fig. 1.—Pathognomonic cell of granuloma inguinale. Note rounded and rod-like bodies within intracytoplasmic cysts. Oil-immersion study made in 1939; × 1300.

central rods were relatively plump in respect to their length. These bodies had the typical appearance of Donovan bodies, while the granulation tissue in which they were found was likewise characteristic of granuloma inguinale.

The pathological diagnosis at that time was granuloma inguinale.

The patient received 19 injections of stibophen, 5 cc. each, intramuscularly at approximately four-day intervals until Sept. 14, 1939, at which time the condition was very much improved. After this date she became delinquent a second time.

On Sept. 26, 1940, she returned with greater progression and extension of the granulomatous process than were originally described.

Smears made from the lesions again revealed Donovan bodies.

Treatment with stibophen was reinstituted, and in four months she received 32 doses of 5 cc. each. During the next 10 months, February to November, 1941, she received 23 doses. During this period of 14 months, September, 1940, to November, 1941, she responded to treatment in that most of the granulating ulcerations healed, but fibrosis and chronic edema of the vulva—elephantiasis (esthiomene)—began to appear. This was limited to the right side of the vulva.

During 1942 we saw her four times. The elephantiasis apparently remained stationary and was rather moderate. There were no active granuloma inguinale lesions. She gave birth to a girl during the year, experiencing a normal delivery through the natural birth canal.

On April 29, 1943, she returned to the clinic with active ulcerated, granulomatous lesions, dispersed over the elephantiasic area. Treatment with stibophen was reinstituted, and from this date to Jan. 17, 1944, she received 29 doses of 5 cc. each. The granulating, ulcerated area healed during this period.

On Aug. 16, 1945, she returned with a greater degree of elephantiasis (Fig. 2). There was a small ulcerated area near the vaginal introitus. Stibophen was again given, and from this date to Oct. 19, 1945, she received 23 doses of 5 cc. each. She was admitted to the hospital for a partial vulvectomy. This was done on Oct. 25, 1945. The specimen was sent to the laboratory for microscopic examination. The report was as follows:

Fig. 2.—Elephantiasis of right side of vulva and extension of granuloma inguinale to left side in 1944.

The skin was composed of stratified squamous epithelium that was entirely normal, showing the usual rete peg and the characteristic differentiation from basal cells to pavement cells, the surface of which was lined in some areas by a thin layer of keratohyalin.

The subcutaneous tissue was the seat of a marked edema and proliferation. The fibrous tissue of the subcutaneous portion was made up of the characteristic fibrous tissue cells and a large amount of collagen matrix. The bundles and strands of collagen were separated in many areas in what appeared to be edema fluid. Scattered throughout the subcutaneous tissue were small bits of smooth muscle. There were numerous vascular elements present throughout the entire subcutaneous tissue, and surrounding these small endothelial elements were collars of inflammatory cells consisting primarily of lymphocytes and plasma cells. This inflammatory process was not characteristic of the usual type seen but rather showed a large predominance of plasma cells with numerous macrophages scattered throughout. Minute examination of the macrophages revealed no evidence of inclusion bodies of the Donovan type; however, the cytoplasm of many of these macrophages gave a somewhat foamy appearance.

The pathological diagnosis was fibrous tissue proliferation with chronic inflammation and edema of the vulva.

She continued to receive stibophen at approximately weekly intervals until Dec. 20, 1945. She then became delinquent again.

On Oct. 7, 1946, she returned with a proliferative and ulcerative process (Fig. 3) which involved the greater part of the vulva. The inguinal regions were not involved, but the process extended forward to the pubic area and posteriorly to the perianal area. The process formed a mass which occluded the introitus of the vagina. The anus and rectum were not involved. A copious serous exudate with a pungent and penetrating odor covered this mass.

Donovan bodies were not found in smears made with material from the lesion.

The reactions to serologic tests for syphilis (Wasserman, Kahn, and Kline) were negative.

It was taken for granted that the patient was having another exacerbation of granuloma inguinale, the disease which had been present in quiescent and active phases since 1938. She was given "anthiomaline" (an antimony and lithium compound) in 3 cc. doses intramuscularly. She received 28 doses from Oct. 7 to Nov. 26, 1946. A little improvement was noted.

Fig. 3.—Lesion of vulva in October, 1946.

On Jan. 17, 1947, she was admitted to the hospital for treatment with streptomycin. Therapy was started on Jan. 23, 1947. She received 62,500 units every three hours for 320 doses. (The dosage was 0.5 gm. per day for 40 days.) A little improvement was noted. This regimen was followed by administration of penicillin, 40,000 units every three hours for 60 doses. After a 10-day respite, penicillin therapy was resumed, and the patient received 20,000 units every three hours for 120 doses, ending on May 3, 1947. The penicillin was given because there appeared to be considerable secondary infection, and whatever improvement occurred was undoubtedly due to the control of this infection.

In the meantime, because her response to antimony and to streptomycin was practically nil, and because the appearance of the lesion was not typically that of granuloma inguinale (Figs. 3 and 4), it became apparent to us that the patient's present problem probably was a malignant growth rather than granuloma inguinale. We sought to have a biopsy specimen taken. This was not done as promptly as desired because those called into consultation and having jurisdiction over the patient in the hospital felt certain that she had granuloma inguinale, and that, therefore, a biopsy would be of little material aid. However, on May 22, 1947, the biopsy was performed, and the report was as follows (Fig. 5).

Microscopic examination of sections made from the lesion of the vulva submitted revealed it to be composed of vulvar and subcutaneous tissue. The epithelial surface demonstrated a

Fig. 4.—Lesion of vulva in January, 1947.

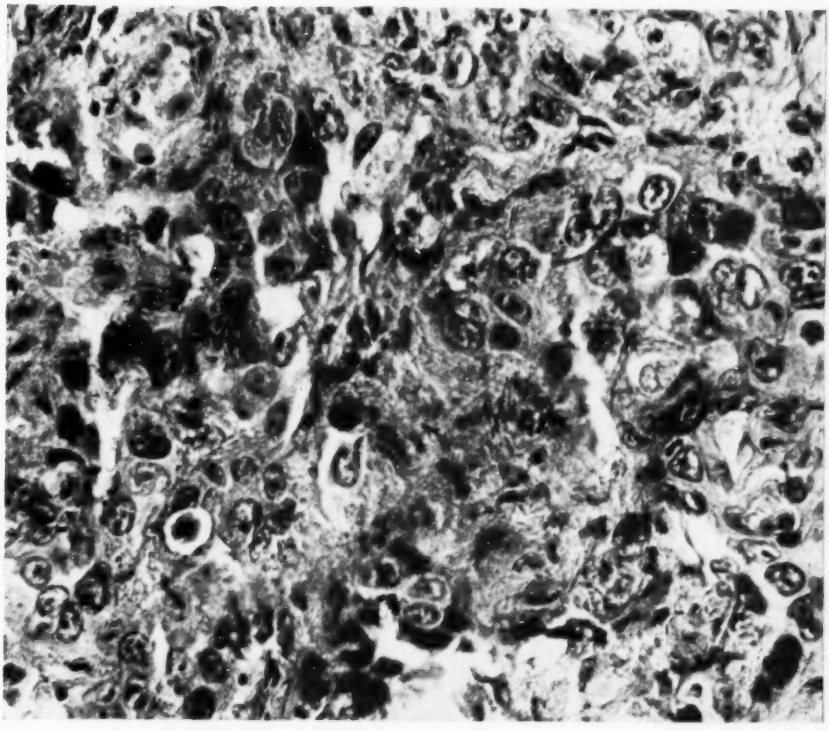

Fig. 5.—Epidermoid carcinoma of vulva, squamous cell type, Grade III.

stratified squamous epithelium which was slightly thickened in focal areas, demonstrative of a minor grade of epithelial hyperplasia. There were prominent brown pigment granules in the cells of the stratum Malpighii.

The tissues of the dermis were infiltrated with cords and irregularly shaped masses of cells arranged in a permanent configuration and extending in some areas almost to the epithelial surface. The cells were large and polyhedral and had abundant pink-staining cytoplasm and round to ovoid nuclei which varied in size, shape, and chromatin content. Many of the nuclei had prominent solid nucleoli, and atypical mitotic figures were noted. Some of the cell nests demonstrated a tendency toward keratinization, but this was not marked. In one area, the cells had a slightly different appearance from the majority of the tumor, demonstrating a more abundant and paler cytoplsm with a pseudoglandular arrangement in some of the areas, suggestive of apocrine gland; even in the areas mentioned, however, there was clear evidence of differentiation of the cells in the direction of squamous cells. Between the clumps of tumor cells, one noted dense trabeculum-like fibrous bundles made up of eosinophilic fibrous tissue.

The pathological diagnosis was epidermoid carcinoma of vulva, squamous cell type, Grade III. She died on Dec. 9, 1947.

COMMENT

This patient was first seen in 1938 with lesions of the vulva and right inguinal region which were diagnosed as granuloma inguinale. The diagnosis was based on the clinical appearance of the lesions and the finding of Donovan bodies in smears made from the lesions. Either because of inadequate treatment owing to delinquency or because of resistance to treatment, the patient experienced, during over a period of years, several exacerbations in the clinical status of this infection. During some of these reactivated phases the diagnosis of granuloma inguinale was reconfirmed by smear and/or biopsy. Also, by biopsy the presence of carcinoma was excluded up to October, 1945, and it was through material taken from the lesions of this patient that the value of the Giemsa stain in demonstrating Donovan bodies in biopsy specimens was proved by Alexander and Schoch [1] in 1940 (Fig. 1.) Another singular fact is that this patient was observed by one of us (L. J. A.) through each of her periods of debility.

Kern [2] in a review of the literature found only three cases in which granuloma inguinale of the genitalia was associated with carcinoma. He questioned the validity of the first case,[3] and he seemed to think that the second case [4] was the same as the first. There is reason to believe that he was correct in assuming or presuming that these two cases were one and the same, but to question the diagnosis is a matter of opinion rather than of fact. (The cervix uteri was the site of involvement in this case or cases.) The third case [5] was that of a 50-year-old Negro having a penile lesion containing Donovan bodies with a biopsy picture of granuloma inguinale. Twenty-three days after the start of therapy with antimony potassium tartrate, biopsy specimens showed squamous cell carcinoma.

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2. Kern, A. B.: Squamous Cell Carcinoma Simulating Granuloma Inguinale, Arch. Dermat. & Syph. **62**:515-525 (Oct.) 1950.

3. Cardwell, E. S., Jr., and Pund, E. R.: Malignancies Related to Venereal Disease: Development of Carcinoma Secondary to Venereal Lymphogranuloma and Granuloma, and Carcinoma, J. M. A. Georgia **29**:60-62 (Feb.) 1940.

4. Pund, E. R.; Greenblatt, R. B., and Huie, G. B.: The Role of the Biopsy in Diagnosis of Venereal Diseases: Histologic Differentiation of Venereal Granuloma and Lymphogranuloma and Chancroid, Am. J. Syph. **22**:495-502 (July) 1938.

5. Lynch, K. M.: Granuloma Inguinale, J. A. M. A. **77**:925 (Sept. 17) 1921.

In this same paper Kern[2] reported on three additional patients with carcinoma of the genitalia, in two of the vulva and in one of the penis, for whom the diagnosis of granuloma inguinale had been made before they came under his observation. He believed the diagnosis of granuloma inguinale was made erroneously in each instance, and that the three patients had carcinoma from the start.

From the foregoing, therefore, it is evident that the subject of this case report is the first patient to be reported in whom development of carcinoma of the vulva secondary to granuloma inguinale of the vulva cannot be questioned.

There should be no doubt that our patient had granuloma inguinale of the vulva for seven or eight years prior to the time carcinoma of the vulva made its appearance. The diagnosis of granuloma inguinale was confirmed by the finding of Donovan bodies in smears and in biopsy specimens on several occasions; also, biopsy specimens had shown no evidence of carcinoma.

In October, 1946, the patient returned to us after a period of delinquency of about one year with a clinical picture of what was thought to be, and glibly accepted as being, a reactivation of her granuloma inguinale. At this time smears for Donovan bodies were negative. She responded slightly to "anthiomaline" therapy. She was given streptomycin, and with this therapy she seemed to improve slightly for a short period. Then the lesion slowly and gradually grew in size and invaded more of the surrounding areas, and the patient's general state went gradually downhill. The appearance of the lesion was no longer that of granuloma inguinale, but rather that of a slowly invasive new growth. On May 22, 1947, a biopsy specimen showed the lesion to be a squamous cell carcinoma.

When did the carcinoma begin? Certainly it must have begun after October, 1945. (Vulvectomy was performed at this time, and microscopic examination of the specimen showed no evidence of carcinoma.) Was the carcinoma present in October, 1946? It probably was. Was granuloma inguinale still present in October, 1946? We think it was. The answers to the last two questions are supported by the fact that the lesion responded in part to "anthiomaline" and streptomycin, and then, after a brief period of improvement, began to progress.

It is, therefore, possible that a patient may have a lesion in which Donovan bodies can be demonstrated and at the same time possess areas of carcinomatous changes of greater or less extent. In other words, the composite picture depends upon which process predominates, upon how long the carcinoma has been present and to what extent it has become the predominating lesion, and upon the sites from which sections are taken for microscopic study. The picture can positively be influenced by treatment for granuloma inguinale, particularly now that antibiotics, such as streptomycin, aureomycin, chloramphenicol (Chloromycetin), and oxytetracycline (Terramycin), are so rapidly effective in granuloma inguinale: In a very short period (a matter of days) the granuloma inguinale part of the mixed lesion (granuloma-inguinale-carcinoma mixture) can be eliminated. The obvious conclusion from this is to perform biopsies promptly on lesions diagnosed as granuloma inguinale that do not at once respond to treatment; to perform biopsies routinely on lesions that offer any doubt as to their true identity before treatment of any sort is instituted.

If there is confusion in diagnosing granuloma inguinale and carcinoma of the genitalia, it is not because the two resemble each other; it is because we are influenced

in favor of granuloma inguinale (1) by virtue of the location of the lesion, (2) by a low index of suspicion of carcinoma, (3) by our failure to realize the two processes may coexist for a period, and (4) by misinterpretation of clinical and laboratory findings.

SUMMARY

A 16-year-old Negro girl was first seen in 1938 with granuloma inguinale of the vulva and right inguinal area. The diagnosis was substantiated by demonstration of Donovan bodies in smears made from material from the lesions.

In 1939 the patient showed a reactivation of the process. The diagnosis was reconfirmed by smear and by biopsy specimens taken from the lesions. Donovan bodies were demonstrated in the smears and in the biopsy specimens.

In 1940, Donovan bodies were demonstrated again in smears made from material from the lesions, which were again active and showed progression and extension of the infection.

She received stibophen (Fuadin) during each of these periods of activity of the process, then more or less sporadically during 1941, 1942, 1943, and 1944, the regularity of treatment depending upon her disposition in the matter. During the period 1941 to 1944 elephantiasis (esthiomene) of the vulva established itself. In 1942, she gave birth to a normal child through the birth canal. No complications or undue difficulties were encountered.

In October, 1945, a partial vulvectomy was performed because of the elephantiasis. Microscopic examination of the specimen removed at this time showed no evidence of carcinoma.

In October, 1946, the patient returned with what was interpreted as being a recurrence of the granulomatous process in all the previously involved areas. Treatment with "anthiolmaline" for two and a half months and then with streptomycin produced only slight improvement. This slight improvement was followed by progression of the process and a general downhill course in the patient's status.

A biopsy specimen taken in May, 1947, showed squamous cell carcinoma.

CONCLUSIONS

The first case in which there can be no doubt that carcinoma of the vulva occurred secondarily to granuloma inguinale of the vulva is reported.

We should encounter less confusion in diagnosing granuloma inguinale and carcinoma if we realized more convincingly that the two processes may coexist, and that during some period one process may predominate over the other.

The predominance or the existence of granuloma inguinale can be readily eliminnated by treatment with the antibiotics streptomycin, aureomycin, chloramphenicol (Chloromycetin), and oxytetracycline (Terramycin).

Prompt biopsy or biopsies should prove the presence or absence of carcinoma.

ADDENDUM

MacKay and Bunch (*Am. J. Syph.* **36:** 511-514 [Nov.] 1952) reported the case of a woman in whom carcinoma of the vulva developed after granuloma inguinale of long duration; they emphasized the fact that this patient was only 32 years old. Our patient was 24 years old when carcinoma of the vulva made its appearance.

MYCOSIS FUNGOIDES

Diagnosis by Aspiration Technique; Observations in Skin and Bone Marrow

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FREDERIC FELDMAN, M.D.
AND
MAURICE MORRISON, M.D.
BROOKLYN

SINCE Stroebel and Hazen in 1911 studied sections of biopsy material of skin in mycosis fungoides and described what they called typical mycosis cells as "measuring from 8-10 microns in diameter and having an eccentric nucleus," the diagnosis of the disease has depended on the finding of these cells.[1] As hematologists, we have been interested primarily in cytology, and our interest has not been confined to the study of blood cells. Starting with the aspiration of bone marrow, we have evolved a simple technique for diagnosis of various diseases, at first, by aspiration from the spleen in many hematological disorders, notably osteosclerotic anemia,[2] Gaucher's disease, Hodgkin's disease, and Boeck's sarcoid,[3] thence to aspiration of lymph nodes for similar hematological disorders,[4] as well as for such malignant conditions as metastatic carcinoma and lymphosarcoma.[5] Our search for cytological material was extended to accessible tumors and to skin lesions. Such diseases as Kaposi-cell sarcoma [6] and lymphoblastoma have been demonstrated by this technique. The various types of cells seen in these and other disorders have been prepared and photographed in color for exhibit.[5]

In the case reported here, the cells seen in the accompanying photomicrograph (Fig. 1) were aspirated from the skin lesion by the simple use of a dry syringe and a 20-gauge needle. The needle is inserted diagonally into the lesion; negative pressure is exerted by the syringe, and the aspirate, which is usually no more than

From the Department of Hematology, Jewish Hospital of Brooklyn.

1. Stroebel, E. R., and Hazen, H. H.: Mycosis Fungoides in the Negro, J. Cutan. Dis. **29**:147, 1911.

2. Morrison, M.; Samwick, A. A.; Rubinstein, J.; Swiller, A. I., and Loewe, L.: Spleen Aspiration in Osteosclerosis and Splenic Hematopoieses: Rationale of Splenectomy, Acta haemat. **6**:309, 1951.

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4. Morrison, M.; Samwick, A. A.; Rubinstein, J.; Stich, M., and Loewe, L.: Lymph Node Aspiration, Am. J. Clin. Path. **22**:255, 1952.

5. Morrison, M.; Samwick, A. A.; Rubinstein, J.; Morrison, H.; Stich, M.; Swiller, A. I., and Feldman, S.: Aspiration Technique: Morpho-Cytological Studies, Exhibit at Jewish Sanitarium and Hospital for Chronic Diseases, New York, Sept., 1952.

6. Stich, M.; Eiber, H.; Morrison, M., and Loewe, L.: Cytology of Kaposi Sarcoma, A. M. A. Arch. Dermat. & Syph. **67**:85-91, 1953.

a minute amount of material, is expelled onto a glass slide and smeared out in the same manner as one smears a drop of blood. After the smear is dry, the slide is stained by Wright's stain technique as employed for blood smears. Occasionally better cell definition is obtained by staining with Giemsa's stain after the Wright stain has been washed off.

REPORT OF A CASE

F. K., a 50-year-old white man, was admitted to the Jewish Hospital of Brooklyn on June 10, 1952, with a seven-year history of generalized pruritus which after one and a half years developed into a scaly erythematous eruption. At this time biopsy revealed signs of mycosis fungoides. He received x-ray therapy, with local resolution; however, this was soon followed by a recrudescence. He then received nitrogen mustard (methyl *bis-* or *tris* [β-chloroethyl] amine hydrochloride) intravenously, again with transient resolution. Following this, corticotropin (ACTH) therapy afforded only temporary partial remission; use of antimony afforded no apparent benefit; triethylene melamine caused severe toxic manifestations, and, finally, therapy with isonicotinic acid hydrazide ("rimifon") yielded no results.

His lesions at the time of admission were generalized, manifested by a dry and erythematous infiltrative eruption covered with hyperkeratotic scales. There were infiltrated plaques on the face and scalp, as well as various-sized mushroom-like tumors covered with crusts. Generalized adenopathy was present.

Peripheral blood studies revealed a polynucleosis with marked toxic granulation: Hemoglobin concentration was 11.5 gm. per 100 cc. (77%), with 4,070,000 red blood cells and 7,750 white blood cells per cubic millimeter. Thrombocytes (platelets) numbered 150,000 per cubic millimeter. There were 10% staff cells, 75% neutrophiles, 4% eosinophiles, 4% monocytes, and 9% lymphocytes.

An aspirate from the skin lesion revealed irregular clumps of cells with nuclei of irregular size and shape. The cells showed various degrees of maturation. There was metamorphosis from a smaller round cell with a distinct well-stained nucleus to a large flat poorly stained cell with absent nuclei, representing desquamation.

Those cells which were intact were rounded or oval and slightly larger than a polymorphonuclear leucocyte, with a round or variably deformed nucleus and more abundant cytoplasm than that of a lymphocyte. The nucleus was dark and basophilic. The cytoplasm was a lighter blue and homogeneously clear (Fig. 1).

The bone marrow showed a shift to the left of the granulocytic elements, toxic granulations of the polymorphonuclear leucocytes, a compensatory increase in the number of erythroblasts, a significant increase in the number of plasma cells, and a number of large reticulum-like cells bearing a marked resemblance to those seen in the skin aspirate (Fig. 2). Megakaryocytes were adequately represented. The granulocyte-erythroblast ratio was 70:30; the granulocyte-polymorphonuclear cell ratio was also 70:30, and granulocytes were present as follows: 35% neutrophilic myelocytes, 5% eosinophilic myelocytes, 15% metamyelocytes, 15% staff forms, 27% neutrophilic polymorphonuclear forms, and 3% eosinophilic polymorphonuclear forms.

Mycosis fungoides is a chronic disease the course of which is marked by four definite stages: dermatitis, infiltration, tumor formation, and ulceration. It is usually limited to the skin, but any organ or tissue may be involved.[7] Local or general adenopathy may be present and indeed may be common, but according to the literature the lymph nodes show no specific changes. Gates noted many cases in which internal metastases in the form of mycosis fungoides were present.[8] Tilley and Smith studied bone marrow smears from six patients with mycosis fungoides and could not confirm the presence of reticuloendothelial reaction reported by other

7. Ormsby, O. S., and Finnerud, C. W.: Mycosis Fungoides: Report of a Case with Autopsy, Arch. Dermat. & Syph. **27**:631, 1933.

8. Cited by Ormsby, O. S., and Montgomery, H.: Diseases of the Skin, Ed. 7, Philadelphia, Lea & Febiger, 1948, p. 867.

Fig. 1.—Mycosis fungoides cells aspirated from skin lesion; × 2100.

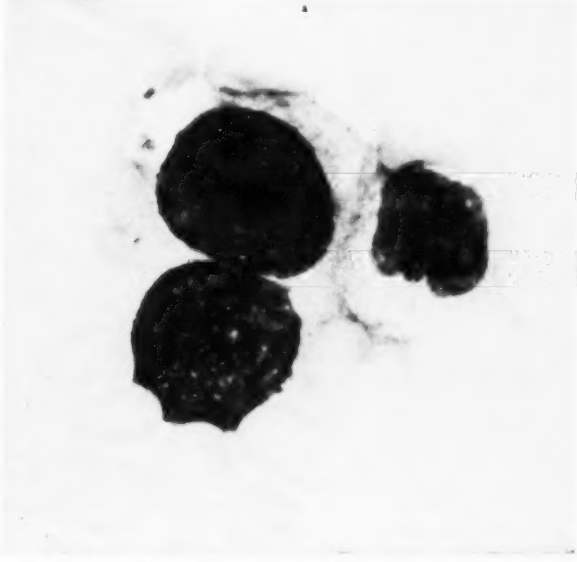

Fig. 2.—Mycosis fungoides cells aspirated from bone marrow; × 2000.

investigators.[8] In our case the bone marrow showed a definite reticulum-type cell, different from the usual type of reticulum cell in its appearance and very closely resembling the cells aspirated from the skin lesion. Sutton and Sutton described this distinct cell type in the premycotic stage of the lesion, i. e., before necrosis has set in, as large, oval, fusiform, or rounded connective tissue cells containing a granular cytoplasm, a large nucleus the chromatin network and nuclear membrane of which are darkly stained, and a more densely stained nucleoplasm.[9] Having had the opportunity to study the cells under higher magnification by oil-immersion microscopy, we are prepared to say that the cytoplasm is not granular, but homogeneously clear. Lever referred to the mycosis cells as immature and atypical histiocytes, differing from mature histiocytes by having larger and more irregularly shaped and deeply stained nuclei.[10] This description coincides with our observation.

SUMMARY

By the aspiration technique described, typical mycosis cells have been aspirated directly from the skin lesion in a case of mycosis fungoides and similar cells have been seen in the bone marrow. This method constitutes a simple office procedure for making a diagnosis and opens up new avenues for detection of other skin lesions.

9. Sutton, R. L., and Sutton, R. L., Jr.: Handbook of Diseases of the Skin, St. Louis, C. V. Mosby Company, 1949, p. 657.

10. Lever, W. F.: Histopathology of Skin, Philadelphia, J. B. Lippincott Company, 1949, p. 424.

LICHEN AMYLOIDOSUS ASSOCIATED WITH VARICOSE VEINS

MAX WOLF, M.D.
NEW YORK

THE PREDILECTION of lichen chronicus simplex, lichen planus verrucosus, and localized primary amyloidosis for certain areas of the legs is frequently dependent on the concomitant state of an impaired venous circulation. These dermatoses may manifest themselves as grouped nodular elevations or as large well-defined thickened plaques. Extensive hyperkeratosis may change their familiar features, and it may become difficult to differentiate them clinically. Examination of the patient in the standing position may reveal the topographic relation of the cutaneous manifestations to the varicosities. The dilated veins may be detected better by palpation than by inspection or with the help of a tourniquet.[1]

Lichen chronicus simplex associated with varicose veins can be beneficially influenced by treatment of the incompetent veins. Involution or complete remission of the annoying skin disorder may be achieved exclusively by this therapy in certain cases. Heyerdale and Cannon[2] were the first to emphasize the advantages of this treatment. Causal relationship between hypertrophic lichen planus and surrounding varicose veins was reported by Dennie and Coombs.[3] These authors assumed that in their patient the poor circulation was the principal factor in the development of lichen planus hypertrophicus, since the lesion cleared twice when better circulation was established.

I had the opportunity to observe a case of localized primary amyloidosis in close connection with varicosities in which the cutaneous eruption responded favorably to the elimination of the deficient venous channels. Since there is no reference in the literature to such therapy in localized amyloidosis, this report is presented.

REPORT OF A CASE

A man, aged 63, had a skin disorder on his legs of 35 years' duration, which was accompanied with excessive pruritus. He was active for his age, and his general health was not affected. The patient's past history and family history were irrelevant.

From the Department of Dermatology and Syphilology of the New York University Post-Graduate Medical School, Dr. Marion B. Sulzberger, Chairman, and the Skin and Cancer Unit of the New York University Hospital.

1. Wolf, M.: Cutaneous and Subcutaneous Lesions of the Lower Limbs in Connection with the Veins: Differential Diagnosis, Arch. Dermat. & Syph. **52**:376 (Nov.-Dec.) 1945.

2. Heyerdale, W., and Cannon, E. E.: Neurodermatitis Associated with Incompetent Greater Saphenous Veins: Report of a Case, Arch. Dermat. & Syph. **44**:52 (July) 1941.

3. Dennie, C. C., and Coombs, F. P.: Lichen Planus Hypertrophicus: Possible Clue to Etiology, Arch. Dermat. & Syph. **61**:121 (Jan.) 1950.

Physical examination revealed no abnormalities, except in the skin and the venous circulation. On the left side of the scrotum and on the left wrist were sharply defined, half-dollar-sized depigmented areas of white atrophic skin. On the middle third of the anterior surface of the right leg there was an eruption, 6 by 11 cm., consisting of closely set hard brownish-yellow hyperkeratotic papules 2 to 3 mm. in diameter. Most of the papules were excoriated and covered

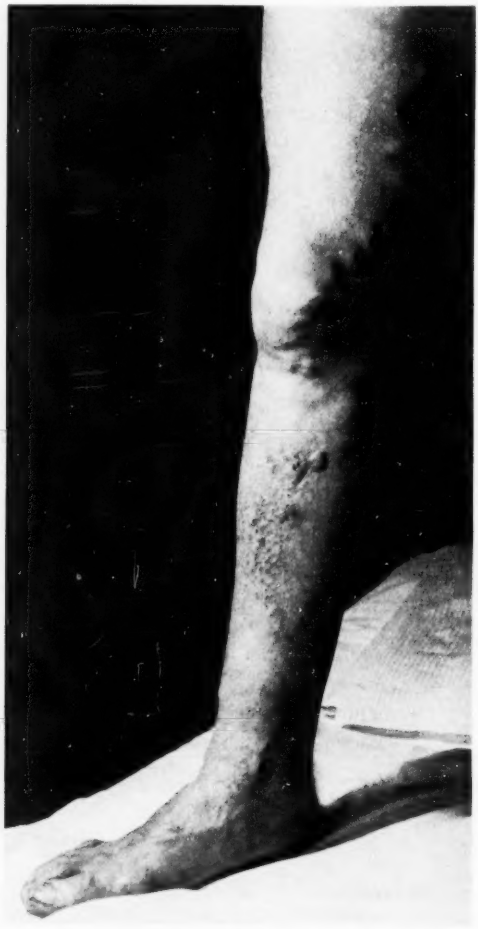

Fig. 1.—Lichen amyloidosus of right leg associated with feeding dilated tributaries of right greater saphenous vein.

by tiny crusts. The papules were not transparent. In the center of the eruption and at the upper pole were two raised, 0.5 cm. thick, infiltrated plaques, grayish brown, hard, and scaly. The tributaries of the right greater saphenous vein were considerably distended and coursed from the middle thigh and beneath the kneecap to the eruption on the right leg (Figs. 1 and 2). Less prominent patches, also surrounded by varicose veins, were found over the middle of the left shin.

Lichen chronicus simplex, hypertrophic lichen planus, and lichen amyloidosus were considered in the differential diagnosis.

The histologic sections, which were studied by M. Jessner, were described as follows:

"The horny layer in three quarters of the specimen is markedly hyperkeratotic, forming several horn-filled depressions extending down in the cutis. The epithelium shows an increased granular layer and an irregular basal layer. The vessels in the upper cutis in the hyperkeratotic

Fig. 2,—Lichen amyloidosus eruption consisting of closely set papules and infiltrated plaques. Close relationship between eruption and varicosities beneath kneecap.

portion are enlarged. Apart from a spotty inflammatory reaction seen best in the papillary bodies, there is a massive infiltration beneath one of the horny depressions. This infiltrate is sharply limited and convex in outline adjacent to the underlying cutis. The infiltration consists mainly of round cells, but contains also fibroblastic elements and some plasma cells. A number of newly formed capillaries is present, and the lower border of the epithelium is loosened in this zone. The massive infiltrate is seen only in the zone beneath one of the horny depressions. A methyl violet

stain for amyloid shows, in the area of the hyperkeratotic part of the specimen, masses of amyloid in the papillary body, especially in the excrescences between the hyperkeratotic depressions."

The histologic diagnosis of hyperkeratotic lichen amyloidosus was based on the changes described.

Fig. 3.—Clinical improvement of lichen amyloidosus nodules and plaques after obliteration of "key veins."

A test for cutaneous amyloidosis was performed by injection of 0.1 cc. of 1% Congo red into a number of the lesions on the left leg. Twenty-four hours later the involved areas of the left leg and the lesions on the right leg (these had not been injected) showed a reddish stain sharply demarcated from the normal skin. The stain persisted for two weeks. An attempt was made to influence the eruption on the right leg and also on the left leg by sclerotherapy of the "key veins" in view of the success with this treatment in localized neurodermatitis associated with varicose veins. Complete suppression of the pruritus in the affected areas was achieved by obliteration of both greater saphenous veins and their tributaries with four injections of Sylnasol

(5% sodium psylliate with 2% benzyl alcohol). There was a striking clinical improvement two weeks after subsidence of the chemically produced inflammation around the veins of the upper thigh and the kneecap. The surface of the hyperkeratotic nodules became smooth; the thickness and roughness of the large plaques were considerably lessened (Fig. 3). The amyloid deposits, however, were not influenced by this therapy. The Congo red tests remained positive. It was decided to treat the residua on the right leg by means of deep curettage with the use of local anesthesia and cryotherapy. The plaques on the left leg were treated in the same way. All lesions healed with atrophic scars.

COMMENT

Primary cutaneous localized amyloidosis, also called lichen amyloidosus, is a rare skin condition. The amyloid may be deposited on any part of the cutaneous surface, but the areas of predilection are the outer aspects of the legs. It is agreed that localized amyloidosis is recalcitrant to most therapeutic measures, although spontaneous absorption of its lesions has been reported in isolated cases.[4] It seems likely that in the present case the atrophic spots on the left side of scrotum and wrist were former sites of amyloid deposits. These lesions, according to the statement of the patient, were similar to the eruptions on both legs when they first appeared about 30 years ago. The degree and intensity of the itching were the same in the beginning; they had disappeared without therapy about 15 years later, whereas the eruption on the legs became increasingly worse over 35 years. The progressive aggravation of signs and symptoms may have corresponded to the gradually increasing impairment of the circulation.

Lichen amyloidosus is usually widespread, involving extensive portions of the lower extremities. But in the present case the dermatosis on both legs was confined to the region around the shins and appeared to be connected with the feeding dilated veins. Amyloid was not demonstrable in the neighboring healthy skin.

This case lends support to the theory that stasis of the venous circulation plays an important role in the development of lichenoid amyloidosis on the legs. The obvious association of the eruption with deficient venous channels in this patient does not seem to be a coincidence. The dilated tributaries of the greater saphenous vein may be regarded as a precipitating factor in the localization and may have contributed to the pronounced hyperkeratotic changes and to the excessive pruritus. The possibility that earlier correction of the impaired venous circulation could have reversed the process completely cannot be excluded. On the other hand, it is not unexpected that amyloid which had accumulated and was firmly embedded in the connective tissue over many years should not have been gradually reabsorbed after obliteration of the incompetent veins without any further local treatment. The patient showed a presumptive tendency to spontaneous resorption of amyloid deposits in other parts of the body. Sagher,[5] who did experimental studies on the absorption of amyloid, found that the typical site of localized amyloidosis is on certain areas of the legs, the skin here possessing qualities likely to favor amyloidosis. Sagher concluded that the essential factor in the pathogenesis of the disease is apparently a local one at a particular site. He was able to demonstrate that skin flaps originally showing a positive reaction to Congo red and transplanted to an area with negative reaction remained unchanged in the course of three and one-half years.

4. Freudenthal, W.: Amyloid in the Skin, Arch. Dermat. u. Syph. **162**:40, 1930.

5. Sagher, F.: Experimental Study on the Absorption of Amyloid in Localized Amyloidosis by Skin Grafting, Arch. Dermat. & Syph. **53**:342 (April) 1946.

SUMMARY

Stasis of the venous circulation may play an important role in the relatively frequent establishment and persistence of primary localized amyloidosis on the legs. Treatment of the incompetent venous channels was of decided value in the management of one case of lichenoid amyloidosis associated with varicose veins. No conclusions concerning the efficacy of this therapy in similar cases can be drawn from a single observation, and a true evaluation must await further trials in a larger number of cases. At this time it is conjectured that by an early correction of an impaired venous return an extension of lichenoid amyloidosis of the legs may be prevented.

969 Park Ave. (28).

Clinical Notes, New Instruments and Techniques

LUPUS VULGARIS TREATED WITH ISONIAZID

A Preliminary Report

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INDIANAPOLIS

The benefits reported from isoniazid (isonicotinic acid hydrazide) therapy in other tuberculous diseases [1] led to its employment in a resistant case of lupus vulgaris.

REPORT OF A CASE

A 34-year-old Negro woman (W. M.) has been seen intermittently since 1926, because of a persistent, extending patch of lupus vulgaris of the left cheek. Other personal and family history has been unrevealing.

At onset, there was a small, chronic, superficial erosion of the left malar area. By 1931, the lesion was 3 by 1 in. (7.6 by 2.5 cm.), triangular, centrally eroded, crusted, and indurated. By 1946, it showed a verrucous surface, edema, a depigmented central cicatrix, and discrete erythematous peripheral papules which were apple-jelly-colored under diascopic pressure. The process continued active.

The von Pirquet and Mantoux (1:100,000) tests were positive. Repeated sputum examinations, urinalyses, blood serologic tests, complete blood counts, albumin-globulin ratios, and x-ray plates of the chest and bones of the hands and feet and a complete eye examination were negative.

For one month in 1946 and for two months in 1949, recommended doses of vitamin D_2 were taken, without benefit.

Therapy.—On March 8, 1952, twice-daily injections of 0.5 gm. of streptomycin were begun, and on March 18 oral administration of 22½ grains (1.5 gm.) of paraaminosalicylic acid four times daily was added (Fig. 1). After 10 days the latter dose was raised to 30 grains (2 gm.), and after another three days it was increased to 45 grains (3 gm.). This combined therapy was carried out for one month without benefit and was then discontinued.

On April 30, oral administration of isoniazid was begun.[2] Figured at 4 mg. per kilogram of body weight, the dose was 50 mg. four times daily. By the second week of therapy, the patch showed a reduction in edema, and by the fourth week the crusting and erythema had lessened. By the seventh week (Fig. 2) activity had regressed, and the condition has steadily improved during the two and one-half months of this single therapy.

Histopathological Studies.—Sections of tissue excised from the face in 1946 and stained with hematoxylin and eosin (Fig. 3) revealed in the upper and middle corium tubercle formations having centrally placed epithelioid cells and giant cells with a fairly broad peripheral zone composed of lymphocytes and occasional plasma cells. Most of the giant cells were of the Langhans type, with numerous peripherally placed nuclei surrounding a pink-staining cytoplasm. Frank caseation necrosis was not present. A portion of the overlying epidermis was acanthotic and

From the Department of Dermato-Syphilology and the Alembert Winthrop Brayton Skin and Cancer Foundation of the General Hospital, Dr. John Eric Dalton, chairman.

1. Elmendorf, D. F., Jr.; Cawthon, W.; Muschenheim, C., and McDermott, W.: The Absorption, Distribution, Excretion, and Short-Term Toxicity of Isonicotinic Acid Hydrazide (Nydrazid) in Man, Am. Rev. Tuberc. **65**:429, 1952. Bernstein, J.; Lott, W. A.; Steinberg, B. A., and Yale, H. L.: The Chemotherapy of Experimental Tuberculosis: V. Isonicotinic Acid Hydrazide (Nydrazid) and Related Compounds, ibid. **65**:357, 1952. Selikoff, I. J., and Robitzek, E. H.: Tuberculosis Chemotherapy with Hydrazine Derivatives of Isonicotinic Acid, Dis. Chest. **21**:385, 1952.

2. The drug used in this investigation was supplied by Eli Lilly & Company, Indianapolis.

Fig. 1.—Photograph taken March 18, 1952, showing solid patch of lupus vulgaris with edema, thickening, surface crusting, residual depigmented central scar from previous erosion, and scattered discrete diascopy-positive papules at periphery.

Fig. 2.—Photograph taken June 14, 1952, showing marked regression of process as evidenced by disappearance of erythema, absence of edema, flattening of all papular elements, clearing of surface crusting, increase in area of central depigmented residual scar, failure to find apple-jelly-colored points on diascopy, and reduction in size of patch.

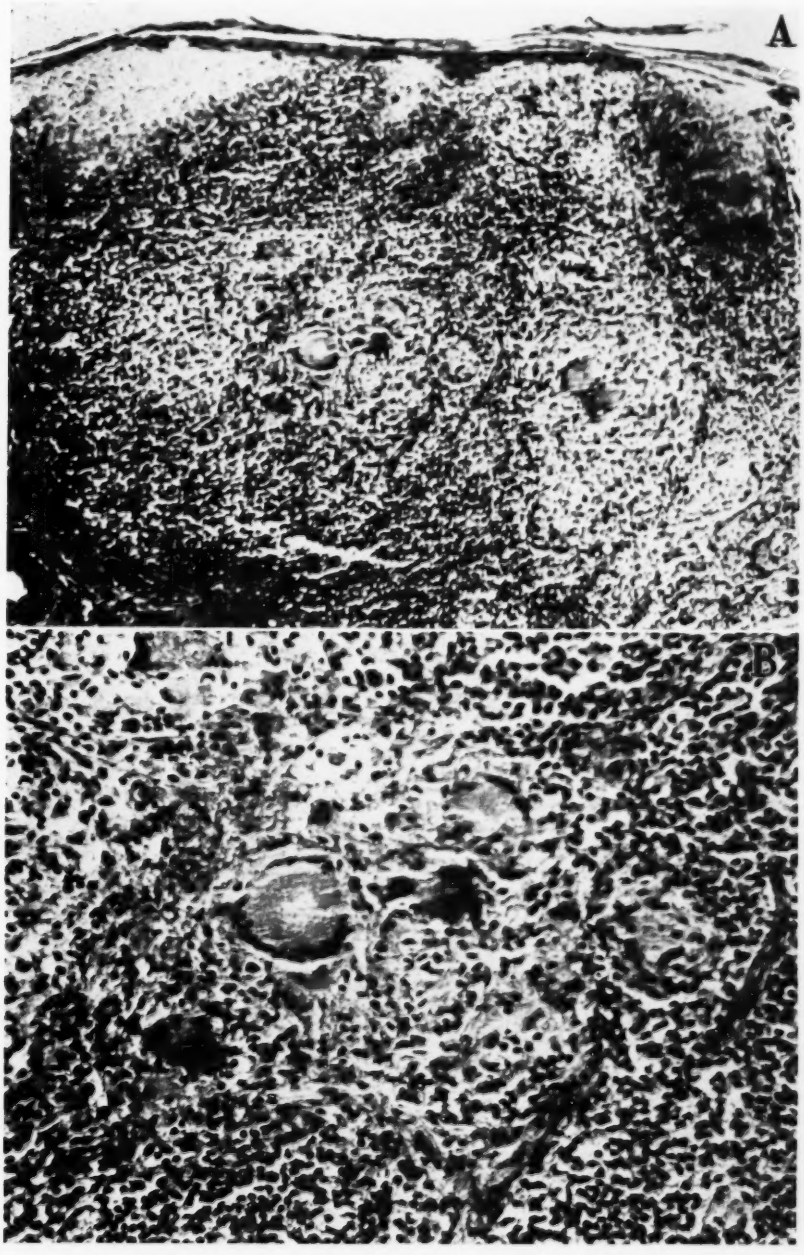

Fig. 3.—*A*, tubercle formation of cutis, biopsy specimen of face, 1946; hematoxylin and eosin stain, × 100. *B* higher magnification, showing tubercle formation; hematoxylin and eosin stain, × 300.

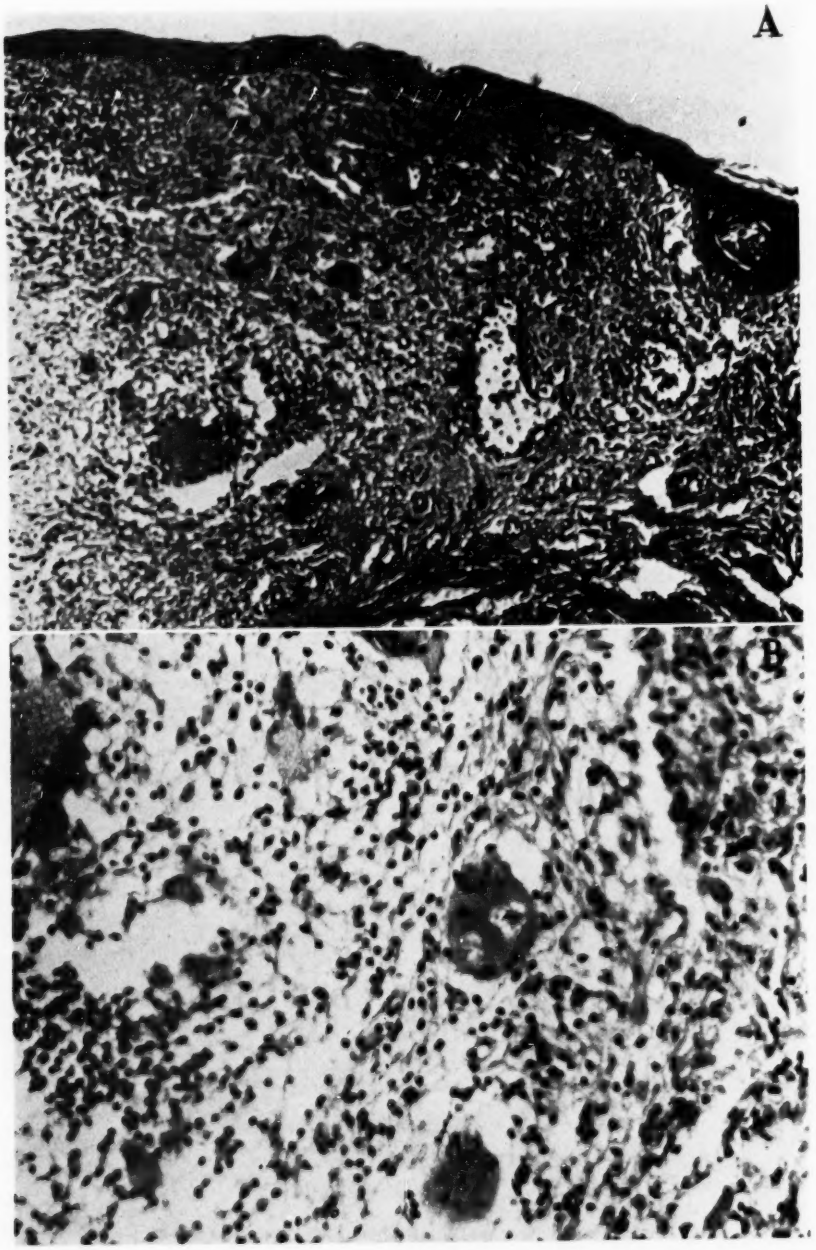

Fig. 4.—*A*, tuberculoid infiltrate of cutis, biopsy specimen of face, March 30, 1952, after streptomycin and paraaminosalicylic acid therapy; hematoxylin and eosin stain, × 100. *B*, higher magnification of *A*, showing asteroid body in a giant cell; × 300.

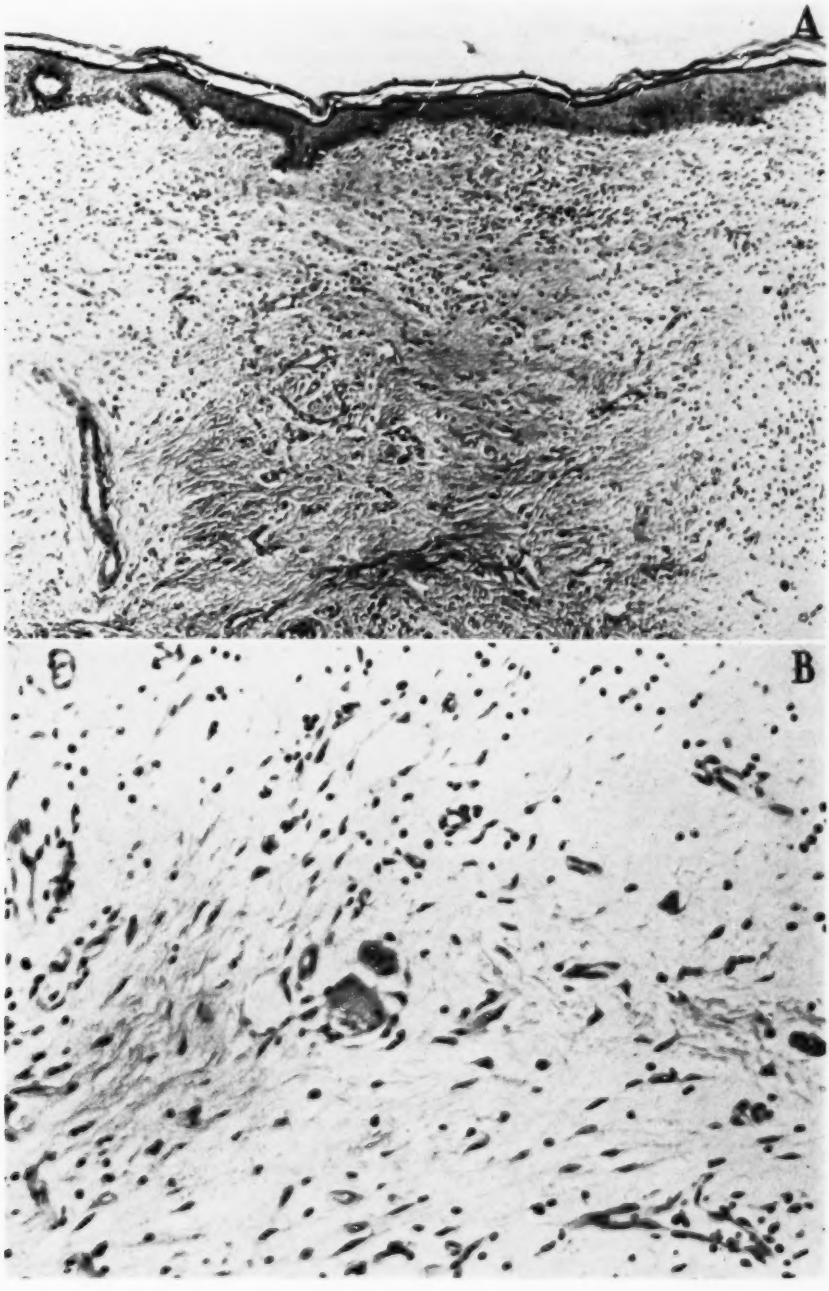

Fig. 5.—*A*, tissue excised from face June 24, 1952, after isoniazid therapy; hematoxylin and eosin stain, × 100. *B*, higher magnification of *A*; × 300.

thickened, while other areas were atrophic and surmounted by parakeratotic cells. Adjacent vascular channels containing red blood cells appeared dilated, and several were surrounded by a mantle of lymphocytes and plasma cells. Adnexal structures were absent in the involved areas. Ziehl-Neelson-stained sections failed to reveal acid-fast organisms. No doubly refractile material could be demonstrated by polariscopic examination, and no asteroid bodies were found.

Similarly stained sections of skin removed from the face in March, 1952 (Fig. 4), and June, 1952 (Fig. 5), did not reveal the well-organized tubercle formation noted in the 1946 sections. The epidermis was markedly thinned, and the corium was edematous and contained scattered foci of chronic inflammatory cells. In places, groups of multinucleated giant cells associated with lymphocytes, plasma cells, and large mononuclear cells without a well-defined tubercle arrangement were seen. An occasional giant cell contained multilocular vacuoles surrounding spiculated structures or asteroid bodies. The last specimen (Fig. 5) revealed a definite reduction in the inflammatory infiltrate. Instead of the fairly obvious tuberculoid structure of the earlier specimen (Fig. 4), there were only occasional loosely knit collections of giant cells in the upper and middle corium. Several spiculated asteroid bodies were seen within multinucleated giant cells. Ziehl-Neelson preparations did not show acid-fast organisms, and no doubly refractile material was demonstrable in the asteroid bodies or other portions of the section.

SUMMARY

In a chronic case of lupus vulgaris, both the clinical and the histopathological findings showed marked regression under treatment with isoniazid. One may question whether this therapeutic result was a primary effect or a supplemental action. This report is but a preliminary one, and the investigation will be carried further with other cases of lupus vulgaris and other forms of cutaneous tuberculosis.

Society Transactions

CHICAGO DERMATOLOGICAL SOCIETY

James R. Webster, M.D., President

Irene Neuhauser, M.D., Secretary

March 19, 1952

Subacute Lupus Erythematosus with a Favorable Response to Quinine. Presented by Dr. Samuel J. Zakon and (by invitation) Dr. Bernard J. Pass.

DISCUSSION

Dr. Stephen Rothman: I learned from Dr. Samuel Becker to treat patients with lupus erythematosus with quinine, starting with a dose of ½ grain (0.03 gm.) of quinine sulfate three times a day and increasing it up to 2 grains (0.13 gm.) three times a day. While we know lupus erythematosus runs a very changeable course, it is my definite impression that quinine is very effective in the symptomatic treatment of disseminated lupus erythematosus. I should like to ask Dr. Becker where this treatment originated and what is its rationale?

Dr. Samuel Becker: I do not know the rationale of quinine treatment. I got it from Stokes at the Mayo Clinic, and I suppose he got it from Dr. Pusey or Dr. Wile. It is in the older literature.

Dr. S. Mercer, Fort Wayne, Ind.: In the past few months I have come to believe that the addition of testosterone to the quinine therapy seems to bring about a more desirable effect.

Dr. James H. Mitchell: When I went into Dr. Ormsby's office in January, 1914, quinine had already been in use for a long time.

Dr. Adolph Rostenberg Jr.: There was recently a note in one of the British medical journals on the use of quinacrine (Atabrine) hydrochloride. It was supposed to have a better effect than quinine.

Dr. Edward A. Oliver: For years at Rush Medical College we used quinine in the treatment of chronic acne vulgaris. If you have a patient with severe acne who has had the limit of x-ray treatments, I suggest that you try administering quinine sulfate internally, 3-grain (0.19 gm.) doses about four times a day.

Dr. Stephen Rothman: What Dr. Oliver says about the use of quinine in chronic acne vulgaris is interesting. Primaquine, a new antimalarial drug, has been claimed also to benefit severe acne vulgaris.

Dr. Samuel J. Zakon: I want to thank the discussers. The main object in presenting this patient was to show that in spite of the fact that what we found looked like an L.E. cell, we refrained from using either corticotropin (ACTH) or cortisone, and had we used either one credit would have been given for something not deserved.

Keratosis Follicularis—Darier's Disease. Presented by Dr. J. H. Mitchell, Dr. M. H. Ebert, and Dr. C. A. Vander Laan.

Mrs. V. G., aged 52, complains that she has had "slivers" on her palms for as long as she can remember. However, the arms or other parts of the body were never involved. She was given "medicine in drops" as a child, but the lesions on the palms were present before this. About eight years ago a rash appeared on the V of the neck. It was diagnosed as contact dermatitis, and it persisted only a short time.

Three weeks ago a red eruption again appeared on the V of the neck. Itching was minimal. During the past week it has spread to involve large areas of the scalp, arms, trunk, thighs, and back.

The past history is otherwise noncontributory except for "pneumonia" one month ago. The father died at the age of 63 of cancer of unknown location, and the mother is 78 and in good health. There are no siblings and no relatives with a similar skin disease.

Punctate keratoses are present on the ulnar aspect of the palms, showing a central raised plug which can be lifted off quite easily. On the anterior chest is an area of pink 3 to 5 mm.

papules, some of them showing excoriations. Over the trunk, and especially across the shoulder area, are numerous brown raised and crusted lesions 2 to 4 mm. in diameter. There are similar lesions scattered throughout the scalp as well as on the arms and legs. Involved areas have a "nutmeg grater" sensation on palpation.

A biopsy frozen section is presented.

DISCUSSION

DR. STEPHEN ROTHMAN: I should like to ask Dr. Pinkus whether it is usual to see lesions around the fingers?

DR. HERMANN PINKUS, Monroe, Mich.: I do not think I can answer Dr. Rothman's question. After all, the lesions are perifollicular and not follicular. I would wonder whether the sweat glands would not also be involved.

DR. CORNELIUS VANDER LAAN (by invitation): The section is typical of the disease. The patient was presented because of her interesting history. The punctate lesions on the palms have been present for many years, while the severe generalized eruption is of only three weeks' duration.

Maduromycosis (Right Sole of Young Woman). Presented by DR. FRANCIS E. SENEAR, DR. LEONARD A. BECKER (by invitation), and DR. RAYMOND R. SIMPSON.

DISCUSSION

DR. IRENE NEUHAUSER: I think that most of us have been intimidated by these cases of maduromycosis because of the large number of organisms which have been attributed to the etiology. It is the opinion of most mycologists that a number of identical organisms have been given different names. Maduromycosis is of actinomycotic or maduromycotic origin. I think this case probably belongs to the latter group. It is a simple matter to identify the group. By using simple stains one can determine whether the organism has the broad hyphae of the higher fungi or the fine hyphae of the actinomycotic group, which readily breaks up into bacillary and coccoid forms.

The Mexican dermatologists have had considerable success in treating these mycoses with the sulfones. The term Madura foot is a misnomer, since not all cases of maduromycosis occur on the feet. In Mexico, where this disease is quite common, one frequently sees other parts of the body involved, especially the back. We should abandon the term Madura foot.

DR. A. H. SLEPYAN: Dr. Neuhauser's appeal to get rid of the term Madura foot is certainly a good idea. I studied one of these patients for about 15 months when I was in Saipan. The patient had a number of draining sinuses on his right foot, and x-ray findings showed bone changes of chronic osteomyelitis. When he was first seen each morning, there were large clusters of ocher-colored, fish-egg-like bodies on his bandage. On direct examination both the ray fungus and long thin filamentous threads were easily found. Repeated attempts at culture proved futile. We administered 300,000 units of penicillin daily along with sulfathiazole by mouth, and the eruption cleared. We were able to follow his case for six months. The sinuses remained dry, and there were no signs of further activity.

DR. M. R. CARO: This patient was seen on the orthopedic service, about five years ago, with a lesion on the foot which had the appearance that this has today, and it was excised, with the clinical diagnosis of tumor. The patient was then lost sight of until last week. She has not been away from Chicago since 1940. The question arises of where could she have picked up such an infection. A roentgenogram of the foot shows no changes in the bone at present.

Xeroderma Pigmentosum in a 6-Year-Old Girl. Previously presented by DR. F. E. SENEAR and STAFF (on Jan. 19, 1949).

DISCUSSION

DR. STEPHEN ROTHMAN: This is a classic case of xeroderma pigmentosum. It is difficult to interpret the reactions to ultraviolet rays that these patients show. No one really knows whether sunburn erythema develops in them with greater ease than in normal persons, although I published a case in 1923, in which I noted that telangiectasia develops much more readily than in normal persons after ultraviolet irradiation.

I think that with a very efficient sun-screening preparation one could do a life-saving job with this child. It is, of course, important to know whether in this disease the unusual skin reaction to light is always restricted to the usual sunburn range of wave lengths.

I should like to ask whether there is a history of consanguinity in this case.

DR. MILTON ROBIN: There is no history of consanguinity.

Pseudopelade. Presented by DR. STEPHEN ROTHMAN and (by invitation) DR. JAMES K. TOMPKINS.

W. M. M., a 34-year-old tailor, first noted a small bald patch on the midanterior portion of his scalp approximately two years ago. This lesion enlarged slowly, and then he noted new similar lesions along the midline extending back to the vertex of his scalp. Lesions began with erythema, and in some of the areas there was some oozing and crusting, but no real pustules. He states that the lesions were asymptomatic, except for slight tenderness at times. After six months the crusting subsided and healed, but new bald spots continued to appear and the old lesions enlarged. One year ago the process halted and remained quiescent until two months ago, when he began to note spreading of the process down the sides of the scalp, without crusting or pustulation.

Treatment has consisted of use of ointments, lotions, and ultraviolet light without benefit.

There are many 1 to 4 cm. circumscribed shiny atrophic hairless scars throughout the top of the scalp from the vertex to the forehead. No follicular openings are seen in the scars. The rest of the physical examination showed conditions within normal limits.

Laboratory findings were noncontributory.

Microscopic examination revealed slight edema of the epidermal cells. No hair follicles were seen in the section, though there were some residual pilomotor muscles. There was a perivascular chronic inflammatory reaction.

Folliculitis Decalvans Onychomycosis. Presented (by invitation) by DR. CALVIN J. DILLAHA and DR. JAMES K. TOMPKINS.

A 26-year-old student from India first noted a pustular eruption on the top of his scalp approximately 10 years ago. These lesions healed without scarring and permanent loss of hair. The process lasted for five years and has remained quiescent since that time. During the course of his disease the patient resided in India and received several different kinds of local medications, none of which altered the course of his disease.

For the past two years he has had progressive involvement of the nails of the left hand with a fungous infection. He has treated these with fungicidal ointments that he received elsewhere, without any response.

Physical examination revealed irregularly shaped confluent areas of baldness on upper posterior aspect of the scalp. The bald skin showed atrophy with hyperpigmentation and depigmentation and absence of follicles. Along the edges of these lesions there were elevated indurated ridges and nodules.

There is discoloration, scaling, and deformity of the fingernails of the left hand.

Laboratory findings were as follows: White blood cells 7,500; hemoglobin 14.5 gm. The Kahn test was negative. Urinalysis showed negative results. Sabouraud cultures of nail scrapings showed Trichophyton rubrum. A KOH preparation was positive for fungi. Under Wood's light the hairs did not fluoresce. Cultures of hair on Sabouraud medium (taken March 12, 1952) showed no growth as yet. A KOH preparation of hair was negative for fungi.

Microscopic examination revealed slight hyperkeratosis. The basal layer was heavily pigmented. The corium was thinned and showed areas of fibrosis. There was one group of follicles present, but these were distorted follicles surrounded by fibrosis, and there were no hair shafts and no sebaceous glands.

At one end of the section there was an area of chronic inflammation with scarring, where there were fibroblasts, lymphocytes, and histiocytes surrounding some pigment granules, presumably the site of a destroyed hair.

With periodic acid-Schiff stain no organisms were seen, apart from bottle bacilli in surface keratin.

A Case for Diagnosis: Erythrasma; Folliculitis with Alopecia? Presented by Dr. Theodore Cornbleet, Dr. David Cohen, and (by invitation) Dr. J. F. Sickley.

The patient is a 67-year-old white man. In 1934 he was bothered with "itching in his head" and was given a liquid "poison" to apply to his scalp. Apparently the patient applied too concentrated a solution of the medication, and a burn resulted. Since this time there has been a permanent patchy alopecia. The patient states that at the time of this treatment there were no "crusts or scales" on his scalp.

About four months ago a generalized itching developed which seemed to be severest about the arms. So far as he knows, he never has had a "skin eruption."

Since 1949 he has been taking "shots for arthritis." He also takes "pills" for this same ailment.

At present, the patient has a patchy complete alopecia of the scalp. Atrophy of the involved skin is apparent.

On the hairy portions of the arms there is also a patchy alopecia. Hair stubbles can be found in these areas. There are a few similar areas on the legs. On the back there are a few excoriations.

In the crural region there is a sharply defined scaling dermatitis showing peripheral activity. In each axilla there is a superficial brownish sharply defined scaling dermatitis.

Urinalysis showed negative results. The serologic reaction was negative. Biopsy of a specimen from the forearm showed nonspecific folliculitis.

DISCUSSION OF THE PRECEDING THREE CASES

Dr. S. J. Zakon: It is very unusual at one meeting to see three cases of cicatricial alopecia: pseudopelade, folliculitis decalvans, and folliculitis with alopecia. The presence of follicular inflammatory papules and pustules is essential for a diagnosis of folliculitis decalvans. However, in cases of long duration the inflammatory papulopustules may be absent, and then one cannot state whether one is dealing with pseudopelade or folliculitis decalvans. I often wondered whether we are dealing with different degrees of inflammation in these two diseases, i. e., one of inflammation and cicatrization without suppuration and one of inflammation, suppuration, and cicatrization.

Dr. H. J. Parkhurst, Toledo, Ohio: I was struck with the resemblance of the scalp condition in the first patient to the end-results of an old favus, especially in view of the fact that the patient had been in Europe in 1945.

Dr. James H. Mitchell: I thought of the possibility of an old favus in the first patient. If it is not that, it is an extremely rare case, because almost all the patients I have seen with pseudopelade have been women, which makes this a very rare case to me. A young woman came to me recently with lichen simplex chronicus in the usual suboccipital area. I think it is interesting that the French speak of pelade as pseudopelade, and we have adopted the word pseudopelade almost exclusively, but we apply it to cicatricial alopecia.

Dr. Marcus R. Caro: The case of pseudopelade shows what Savill has referred to as patches of baldness resembling "footsteps in the snow." I have under treatment at present a patient with pseudopelade, and as the hair is lost there are also produced patches of "footsteps in the snow."

Dr. Irene Neuhauser: Erythrasma is probably much commoner than we suppose, because we do not bother to look for the causative organism. A simple method is to examine the patches with Wood's light. The affected areas fluoresce a beautiful coral color.

Dr. Theodore Cornbleet: We cannot show that our patient has favus and he steadfastly maintains the alopecia occurred after the use of some sort of liquid on the scalp. The keratotic formation there is odd, indeed, but the histopathologic changes shed no light on its nature, being of a nonspecific character. Dr. Laymon's diagnosis of pseudopelade is interesting and maybe even extraordinary, since he thinks the same label may be extended to cover the changes present on the forearms.

Hereditary Hemorrhagic Telangiectasia. Presented by DR. DAVID OMENS and (by invitation) DR. HAROLD D. OMENS and DR. JEROME F. SICKLEY.

DISCUSSION

DR. M. J. BRUNNER: With regard to the patient who had the spider nevi and erythema palmaris, I think the subject has been worked over in previous discussions. This is a brief review. The condition apparently results from an excessive action of estrogen on the superficial vessels in the skin. The reason one sees erythema palmaris and spider nevi in patients with liver disease is that the liver is the organ that normally removes the estrogen from the blood. In defective liver function the estrogen piles up in the blood stream, and eventually such a high level is reached that the effect on the blood vessels is visible. Similar capillary lesions in the skin can develop as a result of estrogen injections. They are also seen in pregnancy, when high levels of estrogen are present.

DR. STEPHEN ROTHMAN: It is not quite clear to me how it can be proved that the vascular dilatation behind red palms or spider nevi is caused entirely by estrogen. Maybe Dr. Brunner has some explanation. I think that the occurrence of these lesions in liver cirrhosis can possibly be explained by increased venous pressure, which is also present in pregnancy. There is probably some congenital vascular weakness of certain parts of the body that predisposes to these lesions—latent spider nevi or red palms, so to speak.

DR. M. J. BRUNNER: I do not have any evidence in support of the theory that estrogen starts these conditions. There are some salient factors. 1. It is known that estrogen can produce an effect on some blood vessels, because that is a normal effect on the blood vessels in the uterus. In pregnancy the uterine blood vessels become markedly dilated. 2. As far as the caput medusae is concerned, I think every one accepts the fact that the dilated veins in the abdomen in a patient with cirrhosis of the liver result from interference with venous return and have nothing to do with hormones. 3. If spider nevi are due to pressure, you should find they are commoner in the lower part of the body than the upper. In an article published in *Medicine* it was pointed out that one never sees spider nevi below the level of the umbilicus. Finally, one can produce spider nevi by administration of sex hormones. This was observed in the treatment of women who had menstrual disturbances. So neither pregnancy, nor liver disease, nor the presence of increased globulin in the blood, and other associated features which were formerly thought to have a direct relationship with spider nevi can be presumed to be the actual cause.

DR. ADOLPH ROSTENBERG JR.: There is evidence against the estrogen theory. Women have now applied estrogens topically for years, and so far as I know there has not been local development of nevi at the site of application of these creams.

DR. THEODORE CORNBLEET: Something to correlate with this is the shape of the estrogen curve and the appearance and disappearance of those capillary changes in the course of pregnancy. There often is some residue of these blood vessel changes after the conclusion of pregnancy or irreversibility.

DR. STEPHEN ROTHMAN: As far as the question of the upper part of the body being involved and the lower part not, I think that this can be explained by the necessity of having an anlage for these lesions. Thus, one will not get red palms or spider nevi in any place from either increased estrogen or venous pressure unless there is a local congenital predisposing factor.

Generalized Granulomatous Folliculitis: Tuberculid? Presented by DR. THEODORE CORNBLEET, DR. HENRY C. SCHORR, and (by invitation) DR. JEROME F. SICKLEY.

The patient is a 55-year-old white woman. Prior to one year ago she had no trouble with her skin. About one year ago she "felt blackheads" over the lower spine. She paid little attention to the lesions until she noted that "pimples" appeared over the anterior chest wall. About four months ago she consulted a physician and was given "pills to take" and a lotion to apply locally. Despite therapy, the eruption continued to spread.

There is no history of drug ingestion prior to the onset of the eruption and no history of "shots."

The patient's only complaint is occasional itching. There is no history of hay fever, asthma, or urticaria.

At present the patient has a generalized eruption consisting of small brownish keratotic lesions. The eruption is most marked about the torso. The face and scalp are clear, but the patient states that her scalp "itches."

There are no nail changes, except for a few transverse striations. The dorsa of the fingers show no lesions.

The mucous membranes of the mouth and throat are clear, except for a small patch of leucoplakia on the left cheek.

Urinalysis showed negative results. The serologic reaction was negative. The reaction to the Mantoux test (1 : 1000) was negative. A chest x-ray showed nothing significant. A skin biopsy revealed folliculitis with tuberculoid infiltrate.

The nonprotein nitrogen was 26 mg. per 100 cc.; the fasting blood sugar 105 mg. Total protein was 7.8 gm. per 100 cc. (albumin 4.9 gm. and globulin 2.9 gm.). Total cholesterol was 178 mg. per 100 cc. The serologic reaction was negative. The reaction to the Mantoux test (1 : 10,000) was negative.

X-rays of the hands showed no evidence of osseous or intra-articular pathology.

The x-ray of the chest showed that there was some hilar adenopathy, more marked on the right. The lung fields were otherwise essentially clear. There was increased density in the region of the right paratracheal nodes. A slide from biopsy a specimen from a nodule is presented.

Psoriasis (and Keratoderma Climactericum?) with Onychogryposis. Presented by Dr. Harvey C. Roll.

Xeroderma Pigmentosum in an 8-Year-Old Girl. Presented by Dr. Milton Robin.

Pityriasis Rubra Pilaris (Forme Fruste of Darier). Presented by Dr. Stephen Rothman.

Lichen Simplex Chronicus Resembling Lichen Ruber Moniliformis. Presented by Dr. Malcolm C. Spencer.

Multiple Basal Cell Carcinomata and Superficial Benign Epitheliomata. Presented by Dr. Edward A. Oliver.

Circumscribed Scleroderma. Presented by Dr. Allan L. Lorincz (by invitation).

Epidermolysis Bullosa Simplex (Recurrent Bullous Eruption of the Feet and Hands [Weber-Cockayne]). Presented by Dr. Louise E. Tays.

Schamberg's Disease. Presented by Dr. Malcolm C. Spencer.

Pityriasis Lichenoides et Varioliformis Acuta. Presented by Dr. Clark W. Finnerud and Dr. Frederick J. Szymanski.

Parapsoriasis Guttata with Leucoderma in a Three and a Half-Year-Old Boy. Presented (by invitation) by Dr. Allan L. Lorincz.

Spider Nevi and Erythema Palmaris; Cirrhosis of the Liver. Presented by Dr. Herbert Ratiner, Dr. Herman H. Rodin, and (by invitation) Dr. Stefan Bielinski.

Sarcoidosis? Presented by Dr. James R. Webster, Dr. Samuel Bluefarb, and (by invitation) Dr. Stefan Bielinski.

Purpura of the Legs Associated with Myeloid Metaplasia. Presented by Dr. James Webster, Dr. Samuel Bluefarb, and (by invitation) Dr. Stefan Bielinski.

Multiple Cutaneous Ulcers; Acute Myelogenous Leukemia. Presented by Dr. James Webster, Dr. Samuel Bluefarb, and (by invitation) Dr. Stefan Bielinski.

Prurigo-like Papular Eruption of the Extremities—Hodgkin's Disease. Presented by Dr. James Webster, Dr. Samuel Bluefarb, and (by invitation) Dr. Stefan Bielinski.

Dermatophytosis(?) of Buttocks. Presented by Dr. Herbert Ratiner, Dr. Harold Rodin, and (by invitation) Dr. Jerome F. Sickley.

Bullous Eruption Cleared with Sulfoxone Sodium (Diasone). Presented by Dr. Theodore Cornbleet, Dr. Henry Schorr, and (by invitation) Dr. Jerome F. Sickley.

Tuberculosis Cutis. Presented by Dr. Theodore Cornbleet, Dr. David Cohen, and (by invitation) Dr. Jerome F. Sickley.

Case for Diagnosis (Tuberculosis Orificialis?). Presented by Dr. Michael Ebert, Dr. Allen Pearl, and (by invitation) Dr. Jerome F. Sickley.

NEW YORK ACADEMY OF MEDICINE, SECTION OF DERMATOLOGY AND SYPHILIS

Annual Residents' Meeting

Anthony C. Cipollaro, M.D., *Chairman*

J. Lowry Miller, M.D., *Secretary*

May 6, 1952

Reticuloendotheliosis (Letterer-Siwe Disease). Presented by Dr. Ralph Teicher.

J. P., an Italian girl aged 16 months, is presented from the Vanderbilt Clinic with anemia and a generalized cutaneous eruption, of one year's duration. She was well except for feeding problems until the age of 5 months, when tonsillitis and a temperature of 103 F. developed. She was given a sulfonamide drug, with the prompt development of a generalized hemorrhagic, vesicular eruption, including the palms and soles. Use of the drug was stopped, with gradual subsidence of the eruption during the next two weeks. At 7 months of age a scaling eruption of

the scalp, eyebrows, and ears developed and persisted despite local therapy. Recurrent attacks of otitis, tonsillitis, and febrile convulsions led to the discovery of a severe anemia and an enlarged spleen. The patient was admitted to Babies' Hospital for study.

The scalp shows a scaling, erythematous eruption which extends over the ears and eyebrows. Within the generalized eruption, papular purpuric lesions 1 to 2 mm. in diameter are seen. On the neck and the anterior and posterior aspects of the trunk there are slightly raised, somewhat greasy-scaled purpuric papules which do not disappear on pressure. The extremities are practically free of any eruption. The child is generally pale. The ears are filled with a purulent exudate. Generalized lymphadenopathy is present. The liver is enlarged 2 cm., and on admission the spleen was palpable 3 cm. below the costal margin.

The hemoglobin was 8.6 gm., and the red blood cell count 2,700,000, with anisocytosis, poikilocytosis, and slight hypochromia. The white blood cells numbered 5,700, with polymorphonuclear leucocytes 48%, lymphocytes 47%, monocytes 3%, and eosinophiles 1%. The red cell fragility was increased and the Rumpel-Leede test positive. The prothrombin time was 17.6 seconds (control 15 seconds). The serum albumin was 4.1 gm. and globulin 2.5 gm., cholesterol 188 mg., calcium 8.4 mg., and phosphorus 4.1 mg. per 100 cc.; phosphatase was 4.2 units. The erythrocyte sedimentation rate was 40 mm. in one hour. The Mazzini reaction of the blood, the tuberculin and the histoplasmin tests, and the cephalin flocculation reaction were negative. The urine showed a trace of albumin, with 0.9 gm. of bilirubin and 1.40 gm. of urobilinogen per 100 cc. The bone marrow was normal with the exception of considerable erythroid hyperplasia. Cultures from the ears yielded beta hemolytic streptococci and Pseudomonas aeruginosa. Roentgenograms of the skull, left clavicle, both iliums, and both femurs revealed large and small bony defects.

Biopsy of the scalp showed an epidermis thinner than normal. Directly beneath the epithelium the upper one-fourth to one-half of the dermis showed almost continuous infiltration by abnormal cells, which surrounded some of the normal accessory skin structures but had not invaded them. Most of these cells were of the large mononuclear variety, but they varied in size. They appeared to form a reticular network. Their cytoplasm stained light-pink. Some of them had somewhat foamy cytoplasm. The nuclei contained abundant chromatin and stained light purple, being of various sizes and shapes. Some were round, ovoid, or kidney-shaped, others irregular; some were placed centrally, others eccentrically. Occasional lymphocytes and rare polymorphonuclear cells were present. In some areas these cells had thinned and invaded the epidermis so that only a thin layer of superficial keratin remained. The subcutaneous tissue was normal. Fat stains revealed numerous fine and medium-sized fat droplets in reticulum cells.

A biopsy of the skull revealed similar pathology except for the presence of numerous eosinophiles. The diagnosis was reticuloendotheliosis (Letterer-Siwe disease).

The child's course was an irregular septic one. All the usual antibiotics were given without much influence on the temperature curve. Repeated transfusions failed to bring the hemoglobin above 8 gm. A course of A-methopterin (4-amino-10-N-methylpteroylglutamic acid), 2.5 mg. daily, was given for 17 days with a resulting drop in the white blood cells to 1,500, with polymorphonuclear leucocytes 26%, lymphocytes 69%, and monocytes 5%. Little change was noted in the cutaneous eruption or the size of the liver or spleen. Because of the rapid fall in hemoglobin and the necessity for repeated transfusion, and because of the evidence of increased fragility of the red blood cells, it was felt that hypersplenism might be partially accounting for this patient's anemia, especially since the bone marrow was extremely active. Splenectomy was therefore performed with the hope of slowing down the need for transfusions. The patient tolerated the procedure well.

Corticotropin (ACTH) and cortisone have not been given in view of her numerous pyogenic complications. The prognosis remains unfavorable.

DISCUSSION

DR. MARION B. SULZBERGER: This is perhaps the third case of Letterer-Siwe disease that I have seen. It is a most interesting and rare entity. Do you think there is any connection between the breaking out of this disease and the sulfonamides she received?

DR. MARGARET HANNIGAN (by invitation): There was a recent report in the literature of the simultaneous occurrence of the condition in twins. One patient was kept as a control and the other treated with antibiotics; the treated patient improved greatly, and it was felt that

aureomycin was responsible. It was therefore administered to the other child, and both have now survived to the age of 3 years, whereas no patient has previously survived more than two years, according to the literature.

DR. HARRY VAN VELSOR (by invitation): In the cases that Dr. Hannigan mentioned the patients were treated with combinations of all the broad-spectrum antibiotics, plus dihydrostreptomycin and penicillin. We feel that with a disease of this type, and most especially cystic disease of the pancreas, the benefit probably comes from the secondary effects, such as nitrogen retention, and not really from the primary antibiotic action of the drugs. We know that aureomycin and chloramphenicol are antagonistic to penicillin when given at the same time; that fact is another point in favor of the belief that the beneficial effects are due to the secondary rather than the primary action of these drugs.

DR. RALPH TEICHER (by invitation): In most of these cases there is some sort of infection at the start, and the patients often receive antibiotics for that infection. The eruption following the use of antibiotics I think is purely Letterer-Siwe disease and entirely coincidental with the administration of the antibiotics. The original concept of this disease was that infection was an etiologic factor as well as a secondary complication, and the fact that antibiotics have proved to have a favorable effect in some cases at least seems to bear out the correctness of that view to some extent. This patient, however, has been given almost every antibiotic, with no effect, and she has also had Aminopterin (4-aminopteroylglutamic acid), but the only result seemed to be depression of her white cell count. Corticotropin and cortisone have been reported from Memorial Hospital as having an ameliorative effect, but they have not yet been given to this child.

Chronic Lymphatic Leukemia with Secondary Leukemid. Presented by DR. JOHN P. RUPPE, JR.

A. S., a man aged 54, is presented from the New York Polyclinic Medical School and Hospital. He has had leukemia for the last eight years, during which time he has been treated periodically with x-ray therapy to the spleen, with good results. About seven weeks ago, after a cold and sore throat, a papulopustular eruption appeared on the face, spread to the chest, and then spread to the extremities. He was admitted to Willard Parker Hospital, where the lesions were not thought to be typical of varicella. Virus studies were negative. A biopsy specimen taken from an intact shrunken vesicle on the right thigh was reported to contain a number of ballooned epithelial cells, whose nuclei did not stain but some of which could still be recognized as multinucleated epithelial cells. A few single-nucleus ballooned cells showed the presence of an inclusion body within the nucleus. The underlying corium showed some broken-up leucocytes. Lymphocytic collections were present around the cutaneous appendages, but there was no diffuse leukemic infiltration of the corium. The pathologist reported that the lesion was of the varicella type. The patient was discharged from Willard Parker Hospital and admitted to the New York Polyclinic Hospital and Medical School.

At present there is a generalized eruption consisting essentially of two types of lesions. The majority are small, flat-topped, light-brown, slightly scaling papules. The remainder are dark, crusted lesions which leave a depressed scar where they have fallen off. The pharynx and tongue are injected, and the left anterior cervical nodes are enlarged. The inguinal nodes are also enlarged, and the liver extends 2 fingerbreadths below the costal margin. The spleen is not palpable.

The findings on urinalysis were normal, and serologic tests for syphilis were negative. The blood urea nitrogen was 14.5 mg. per 100 cc. The erythrocyte sedimentation rate was 35 mm. per hour. The fasting blood sugar was 101 mg. per 100 cc. Blood studies on April 14, 1952, showed 31,600 white cells, with 84% lymphocytes, 11% polymorphonuclears, 1% eosinophiles, and 4% blasts, 2,890,000 red cells, and 10.3 gm. of hemoglobin. On April 19 the values were 54,000 white cells, with 95% lymphocytes and 5% polymorphonuclears, 4,100,000 red cells, and 9.3 gm. of hemoglobin. On April 28 there were 23,400 white cells, 3,200,000 red cells, and 11.4 gm. of hemoglobin. Thrombocytes (platelets) numbered 148,000; the prothrombin time was 38 seconds,. and the total protein was 6 gm.

Biopsy of a flat-topped papule on the forearm showed the vessels to be dilated throughout the upper cutis, with a moderate focal reaction about them. The infiltration was composed of

small round cells and wandering connective tissue cells. The epidermis was thin and showed no important changes. The diagnosis was erythema multiforme type of reaction which might fit in with a leukemid (Dr. Perry Sachs).

The cutaneous lesions have continued to involute slowly, leaving hyperpigmentation and scarring. The leucocytosis has responded to x-ray therapy to the spleen. Pyogenic infections of the ear and pharynx are being controlled with penicillin intramuscularly.

DISCUSSION

DR. MARGARET HANNIGAN (by invitation): In my limited experience I have seen two other cases in which chronic lymphatic leukemia with a generalized eruption was called varicella. I wonder whether that is not a common finding?

DR. MARION B. SULZBERGER: That is a very common finding. As a matter of fact, whenever you see herpes zoster you must think of leukemia.

DR. MAURICE J. COSTELLO: I saw a patient at Willard Parker Hospital with a generalized eruption which was varioliform rather than varicelliform. These eruptions are not uncommon, and they can be varioliform as well as varicelliform.

DR. PERRY SACHS: The biopsy specimen I saw was taken after the vesicular lesions had disappeared. It showed no evidence of any bullous lesion and no suggestion of virus disease but was purely an erythema multiforme type of reaction which is seen in lymphoblastomas, such as leukemia.

DR. ALFRED PELZIG (by invitation): Recently at University Hospital we had a patient with acute myelogenous leukemia with a hemorrhagic bullous infiltrate on the arm. I am wondering what the incidence of vesicular leukemid is in myelogenous leukemia as compared with lymphatic.

DR. J. P. RUPPE (by invitation): One possible explanation of the pustular eruptions in this patient with lymphatic leukemia is that they are related to the very low percentage of polymorphonuclear leucocytes, causing the patient to have a low resistance to all types of infection. We have had to give this patient antibiotics intermittently, once for cellulitis of the finger following a prick for a blood count and later for recurrent streptococcal infections of the throat.

DR. CHARLES WOLF: These toxic eruptions that occur with the lymphoblastomas are frequent, particularly after radiotherapy, and they assume bizarre pictures, such as erythema multiforme, macular eruptions, and all types of dermatitic lesions. The lesions in this patient seem to fit in well with those seen in a person who has received a great deal of radiotherapy. They are a manifestation of the toxic phase, probably a leukemid.

Xanthoma Tuberosum (Essential Familial Hypercholesteremia). Presented by DR. JEAN CRAMER.

M. G., a woman aged 41, is presented from the New York Hospital with asymptomatic, discrete, yellow, raised lesions on the left elbow which were first noted one year ago. She has noted no new lesions since that time. The patient has gained 20 pounds (9.1 kg.) in weight in the past three years, without intolerance to cold or easy fatigability. She has an average dietary history.

The patient reported "Bright's disease" at the age of 7 years, with six weeks of swelling of her body. She was well until a right perinephric abscess was incised at the age of 10. There have been no known urinary abnormalities or liver disease in the interval years. Her mother has angina-like attacks necessitating use of glyceryl trinitrate (nitroglycerine).

There are clustered, firm, yellow papules over the left olecranon, about 1 mm. in diameter, with one 5 mm. lesion. In the palmar creases bilaterally can be seen distinct yellow lines. There is no change in skin texture.

The basal metabolic rate was —15%. The specific gravity of the urine was 1.017, with albumin (1 +) and 1 to 3 red blood cells and 6 to 10 white blood cells per high power field. The blood studies showed hemoglobin 15.4 gm. per 100 cc. and white blood cells 8,000, with lymphocytes 24%, monocytes 12%, mature forms 53%, band forms 10%, and basophiles 1%. Some young monocytes were described on smear. The total cholesterol was 551 mg. and cholesterol esters 346 mg. per 100 cc. or 62.8%.

Lipoprotein fractionations were performed (Barr, Eder, Russ), with use of the Cohn fractionation technic. Almost all the plasma cholesterol can be found in the alpha and beta fractions (25% in the alpha and 75% in the beta fraction). In patients with coronary artery disease, in diabetics, after myocardial infarctions, and in patients with familial hypercholesteremia and xanthomatous disorders in general, there is a drop in the alpha lipoprotein fraction, with a commensurate elevation of the beta fraction. It is felt that the S_f10-20 molecules of Gofman are in the beta lipoprotein fraction of Eder and Barr. This patient demonstrated similar pronounced changes in the two fractions.

DISCUSSION

DR. JEAN CRAMER (by invitation): This patient was presented because of the lipoprotein fractionation studies which are being done on a research basis by Drs. Eder and Barr, at New York Hospital. Their work appears to parallel that of Dr. Gofman, in California, on lipoprotein fractionations in xanthomatous disease, atherosclerosis, diabetes, and other disorders in which elevated serum lipids may be noted. This patient with xanthoma tuberosum shows the typical blood chemical abnormalities seen in this familial disorder; there is a marked drop in the alpha lipoprotein fraction and a rise in the beta lipoprotein fractions, as compared with the values obtained for normal persons.

The significance of these studies is that a similar lipoprotein alteration is seen in persons with severe coronary artery disease and recent myocardial infarcts; they show a rise in the S_f 10-20 molecules, as do diabetics and the xanthoma tuberosum patients, who tend to acquire early and severe atherosclerosis. It is felt that one may be able to predict the development of coronary occlusions by changes in the blood lipids. Persons with xanthomatous disorders should be investigated from this point of view, with electrocardiographic and lipoprotein fractionation studies.

DR. DAVID BLOOM: This looks much more like the eruptive type of xanthoma seen in diabetics. There is nothing in the history regarding the urinary or blood sugar. I think the patient needs investigation regarding diabetes. The picture would fit the eruptive type of xanthoma much more than the tuberous type.

DR. JEAN CRAMER (by invitation): The fasting blood sugar and urinary sugar determinations were within normal limits. Seventy per cent of patients with xanthelasma demonstrate hypercholesteremia, but only 25% of these patients are found to have coronary artery disease. These people with xanthelasma are felt to represent the heterozygous abnormal of essential familial hypercholesteremia, and the xanthoma tuberosum and tendinosum patients, the homozygous abnormal.

Amyloidosis Cutis (Macular). Presented by DR. PAUL P. WESTFALL.

A. R., a Puerto Rican woman aged 33, is presented from the New York City Hospital with yellowish-brown plaques on the sides of the legs, which she first noticed 10 years ago. They gradually became more prominent, the pigment becoming more intense, particularly during the last few months. The patient complains of itching. She has no knowledge of a similar condition in any member of the family. Her blood Wassermann reaction was said to have been positive in 1941. Prior to 1949 she had four spontaneous abortions. She again became pregnant in 1949, and during antepartum care received 10,000,000 units of penicillin. She subsequently delivered a normal, full-term boy.

There are diffuse and confluent, fawn-colored, macular lesions on the tibial and outer surfaces of both legs, on the back of the neck, and on the extensor surfaces of the arms and forearms.

The results of urine, blood chemistry, cholesterol, and Mazzini studies were all within normal limits.

A biopsy specimen examined by Dr. G. F. Machacek showed an attenuated epidermis, the rete pegs of which were widely separated and hyperpigmented. Between these rete pegs, which were slightly elongated, were globular masses of degenerated collagen, which was broken up into homogenous masses. In these areas of degenerated connective tissue could be seen stellate cells, which also contained melanin. The epidermis was also hyperkeratotic. The reticulated cutis was made up of fibers which paralleled the surface and were widely separated. The lesion was evidently one of amyloidosis.

Amyloidosis (Papular). Presented by DR. PAUL P. WESTFALL.

A. G., a Puerto Rican woman aged 36, is presented from the New York City Hospital with extensive pruriginous plaques on the outer aspects of both legs, darker in color than the adjacent nonaffected skin. In the summer of 1951 she first experienced itching along the front of the legs, which spread later to the outer aspects of both ankles. The patient then noted that the itchy areas looked darker and thicker than the surrounding skin. The pruritus caused her to seek medical attention. As a child she had an attack apparently of glomerulonephritis, with swelling of the ankles, periorbital puffiness, and albuminuria. At the age of 24 she received arsphenamine (salvarsan®) or oxophenarsine hydrochloride (mapharsen®) and bismuth for syphilis.

On the anterior and lateral aspects of both legs are noted brown-yellow papules. They vary from the size of a pinhead to that of a split pea and show both discrete and confluent areas.

There was moderate anemia, with 3,320,000 red blood cells and 8.3 gm. of hemoglobin. The albumin in the urine varied from 1 + to a trace. The erythrocyte sedimentation was increased, 35 to 45 minutes by the Cutler method. Serologic tests for syphilis were negative, and roentgenograms of the chest and abdomen were normal.

Biopsy studies by Dr. James R. Lisa and Dr. G. F. Machacek were reported as amyloidosis.

DISCUSSION OF CASES OF AMYLOIDOSIS

DR. HARRY VAN VELSOR (by invitation): A year ago we presented a typical case of lichenoid amyloidosis from St. Luke's Hospital. We injected cortisone into a small area and at first believed that we were getting a dramatic response; however, in a few weeks we saw that the areas covered with adhesive tape responded just as well as did the inoculated areas. We decided to treat the patient with Unna boot dressings and have done so for the past year. At present there is no evidence of lichenoid amyloidosis, which brings up the question in my mind whether neurodermatitis comes first and produces the amyloid deposit, or vice versa.

DR. LAURENCE PALITZ (by invitation): It is interesting to see the macular and papular types of amyloidosis cutis side by side, and one might think the macular form was the precursor. However, the patient with the macular type has had it for 10 years, and, of the two whom Dr. Peck and I presented last year, one had had it for 14 years and the other for 8; hence I do not believe that the macular type will often, if ever, develop into the papular.

DR. F. PHILIP LOWENFISH: I thought it interesting that both women gave a history of syphilis which had been treated; the patient presented from Mount Sinai also gave a history of syphilis. We are trying to discover the role of syphilis in this condition.

DR. PAUL P. WESTFALL (by invitation): Both patients were Puerto Ricans; both were syphilitic with negative serologic reactions at present, and both had itching; there was somewhat similar localization of the lesions in the two cases and in both the diagnosis was confirmed by pathologic study.

Essential Cryoglobulinemia with Purpura. Presented by DR. ALFRED PELZIG.

J. F., a woman aged 33, is presented from the Post-Graduate Medical School of the New York University-Bellevue Medical Center and the Skin and Cancer Unit. Five years ago hives developed on the legs and forearms; these were severer on exposure to cold and dampness. They responded well to tripelennamine. Three years ago in early pregnancy use of the antihistaminic was discontinued. A purplish eruption developed on the legs at this time but cleared with advancing pregnancy. There was a severe exacerbation post partum, with violaceous papules on the legs, arms, and buttocks. These were associated with arthralgia—but without edema—of the ankles, knees, wrists, elbows, and fingers. She was seen at the Skin and Cancer Unit two years ago. Examination revealed papular purpuric lesions on the legs, buttocks, trunk, and arms. Splenomegaly and hepatomegaly were noted.

Serial gastrointestinal and gall-bladder x-ray studies were normal. The Mazzini reaction of the blood was negative. The erythrocyte sedimentation rate, prothrombin time, Rumpel-Leede test, vitamin-C saturation determination, and bleeding and clotting times were normal. The thrombocyte (platelet) count was normal except for one reading of 72,000. In September, 1951, the albumin was 3.0 gm. and globulin 3.3 gm., and in December the basal metabolic rate was + 19%.

The patient was treated with vitamin C, vitamin K, ferrous sulfate, and a protein hydrolysate without result. The lesions still developed most markedly in winter, but they also appeared in summer after exertion.

She was admitted to University Hospital on Jan. 29, 1952, at which time there were discrete, papular, violaceous lentil- to dime-sized lesions on the thighs, buttocks, arms and trunk. They did not fade on pressure and were most elevated at areas of friction from bedclothes. The legs showed reticulated, brownish pigmentation, with scaling and atrophy of the skin. The liver was nontender, and reached the level of the umbilicus; the spleen was felt 3 finger-breadths below the costal margin.

Laboratory examinations at this time showed red blood cells 2,900,000, hemoglobin 7.8 gm., hematocrit 28 per cent, reticulocytes 4.6 per cent, and platelets 125,000. The bleeding time was four minutes and coagulation time five minutes. There were 2,550 white blood cells, with polymorphonuclear leucocytes 53%, lymphocytes 40%, monocytes 6%, and eosinophiles 1%. The erythrocyte sedimentation rate determination was unsatisfactory because of the extremely rapid agglutinations of cells. The prothrombin time was 20 seconds (normal 14 to 16 seconds). The serum bilirubin was 0.42 mg. (normal 1.0 mg.). Total serum proteins were 5.6 gm., with albumin 3.4 gm. and globulin 2.2 gm. (albumin-globulin ratio 1.5). The cephalin flocculation test was negative, and thymol turbidity was 1.0 unit (normal 0 to 4 units). Urinalysis showed 70 to 80 red blood cells per high power field. On Feb. 4, 1952, the red blood cell fragility test showed hemolysis beginning at 0.495% and complete at 0.315%. Cold agglutination was normal. A heterophile antibody test elicited a negative reaction. On Feb. 19, the total serum protein at 37 C. was 5.6 gm. per 100 cc. (albumin 3.1 gm. and globulin 2.5 gm.; albumin-globulin ratio 1.2); at 4 C. the total protein was 4.1 gm. (albumin 3.1 gm., globulin 1.0 gm.; albumin-globulin ratio 3.0); the value for cold-precipitable protein was, therefore, 1.5 gm. per 100 cc. On April 23 the value for total protein was 4.6 gm. per 100 cc. at 37 C. and 4.4 gm. at 4 C.; the value for cryoglobulin was 0.2 gm. per 100 cc.

During the hospital stay new purpuric lesions have developed; these subsided in three days. Purpuric lesions induced by application of ice water to the skin for 1 hour subsided in 36 hours. The patient has been treated with antihistamines, corticotropin (ACTH), and conjugated estrogenic substances (Premarin), without success. New purpuric eruptions in the past month, however, are not as elevated as on admission. During her stay the cryoglobulin level has dropped to 200 mg. per 100 cc. The liver and spleen have diminished in size, although they are still palpable. The erythrocyte sedimentation rate at 37 C. is 129 mm. per hour. Tests for Bence-Jones protein are negative.

Biopsy of a new lesion showed intracapillary clumping of red cells, perivascular infiltrate of polymorphonuclear leucocytes, small round cells, and extravasation of red blood cells into connective tissue. The Perl stain was negative.

Liver biopsy showed mild focal hepatitis; biopsy of the bone marrow showed slight hyperplasia. A muscle biopsy was not diagnostic, nor was a gingival biopsy. Roentgenograms of the skeleton were normal, and findings on cystoscopy and a retrograde pyelogram were likewise normal. On Feb. 15 the total protein was 5.4 gm. per 100 cc. (albumin 2.9 gm., alpha$_1$ globulin 0.6 gm., alpha$_2$ 0.8 gm., beta 0.8 gm., gamma 0.3 gm.).

DISCUSSION

DR. ALFRED PELZIG (by invitation): The reason for the attempt to use corticotropin and estrogens was the development of the eruption early in pregnancy, clearing as the pregnancy advanced and remained clear for a short time post partum. It was also noticed that the lesions seemed to undergo the greatest exacerbation just prior to and during the menses. The steroid therapy was unsuccessful. However, during the patient's hospital stay, the level of the precipitable proteins has dropped and the liver and spleen have decreased in size. The medical department has made no diagnosis for the hepatosplenomegaly. Six other cases of purpura and cryoglobulinemia have been reported.

Sarcoidosis Simulating Lupus Vulgaris. Presented by DR. CONRAD STRITZLER and DR. ZOLTAN RUBIN, from Queens General Hospital, Jamaica, N. Y.

PHILADELPHIA DERMATOLOGICAL SOCIETY

H. E. Twining, M.D., *Chairman*

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April 18, 1952

Chronic Benign Plaques on Mucous Membranes. Presented by Dr. Carroll F. Burgoon Jr.

L. B., a white man aged 22, presents slightly erythematous, annular, and polycyclic lesions with raised white borders located on the buccal and gingival mucous membranes. The lesions have been present continuously over a period of four years.

A blood cell count was within normal limits; roentgenograms of the chest and teeth were normal; the serologic tests for syphilis were negative, and the sedimentation rate was 27 mm. (corrected) per hour. Ear, nose, and throat consultation discovered no evidence of focal infection.

The histologic report stated that the mucosa showed an area of infiltration with acute inflammatory cells. There was a moderate degree of acanthosis and rete peg hypertrophy, and in these areas mitotic figures were not uncommon. The subjacent areas showed mononuclear cell infiltration.

Treatment by diet and with antihistamines was ineffectual.

DISCUSSION

Dr. E. R. Gross, Wilmington, Del.: I think this condition is recurrent aphthous stomatitis, and I suggest the parenteral administration of male hormone as a nonspecific measure.

Dr. Reuben Friedman: I am inclined to agree with the diagnosis of migratory plaques because (1) the lesions on the buccal mucosa do have elevated margins, (2) the patient insists that they have never ulcerated or bled and that they are asymptomatic even when he ingests acid foods or citrus juices, and (3) the lesions are sometimes abundant or are sometimes few, and recur at different sites. They seem, then, to behave as do migratory plaques on the tongue, and while migratory plaques on the buccal mucosa are unusual, I can offer no other diagnosis.

Dr. Carroll F. Burgoon: We have followed this patient closely for well over a year. At no time have there been any erosions of the mucosal surface, and the course of the lesions has been that of benign transitory plaques.

Dr. Thomas Butterworth, Reading, Pa.: Benign plaques on the tongue will frequently disappear under penicillin therapy; it will give temporary relief.

Dr. Douglass A. Decker, Allentown, Pa.: I treated three patients with long-standing aphthous stomatitis with 15 to 30γ of vitamin B_{12} weekly, with satisfactory results.

Alopecia Totalis: Response to Corticotropin (ACTH) and Cortisone. Presented by Dr. Carroll F. Burgoon Jr.

F. V., a white woman aged 30, shows sparse short hairs on the scalp with relatively bald spots in the parietal areas. Axillary and pubic hair, eyebrows, and eyelashes are normal. Patchy bald areas began in the occiput in 1939. The hair loss was associated with severe pain in the occiput with irradiation to the vertex. In 1946, after an appendectomy, the loss of hair progressed until 1948, when practically all the hair, including that of the pubic area and axillae, the eyebrows, and the eyelashes, was lost.

There is nodular enlargement of the right lobe of the thyroid.

A psychiatric consultant made a diagnosis of conversion hysteria.

The serologic tests for syphilis were negative; a complete blood cell count and a roentgenogram of the chest showed normal findings. The Thorn test was positive.

The histologist reported that the scalp (left parietal area) was marked by absence of hair follicles and sebaceous glands, but an occasional rudimentary shaft was noted.

The patient was treated with intravenous injections of corticotropin for 21 days and with cortisone for eight weeks.

Generalized Alopecia: Hydrolyzed Wool Employed in Treatment. Presented by Dr. Joseph V. Klauder and Dr. B. A. Gross, Wilmington, Del.

A. C., a white woman aged 54, was first seen on April 10, 1951, with generalized alopecia. Its onset was in November, 1950, when in the course of two weeks the entire scalp became bald. Hair loss also involved the eyebrows, most of the cilia, the axillae, the pubic region, and the hair on the forearms.

In April, 1951, the following treatment was prescribed and carried out for six months: use of a well-balanced diet, including the yolks of two eggs daily, 3 tablets of brewers' yeast three times daily, a weekly injection of 1 unit of crude liver extract, and daily application to the scalp of an estrogen cream (Premarin 870—0.625 mg. of conjugated estrogenic substances per gram). Two teaspoonfuls of hydrolyzed wool was ingested in a half glass of water after each meal.

In the early part of June, 1951, there was evidence of regrowth of hair. Now the hair of the scalp has sufficiently regrown to give the appearance of a boyish bob. The eyebrows and almost all the cilia have completely regrown. There are sparse hairs in the axillae and on the pubic region. The patient has gained weight, looks generally in a better state of health, and has regained her sense of well-being.

The use of hydrolyzed wool is based on the studies of J. V. Klauder and Herman Brown on sulfur metabolism of the hair, nails, and skin (Sulphur Content of Hair and of Nails in Abnormal States: Therapeutic Value of Hydrolyzed Wool; Hair, Arch. Dermat. & Syph. **27**:584, 1933; II. Nails, ibid. **31**:26, 1935; Certain Phases of Sulphur Metabolism of the Skin, ibid. **34**:568, 1936). The preparation of hydrolyzed wool is detailed in the first of the references. The cystine content is 1.5 gm. per 32 cc.

DISCUSSION

Dr. A. Strauss: In the case presented by Dr. Burgoon there seems to have been an excellent result, but, personally, I should hesitate to continue the use of those drugs because my examination disclosed that as many hairs are developing on the patient's face as on the scalp.

Dr. Herbert M. Leavitt, Easton, Pa.: I had a similar case of alopecia totalis in a woman 65 years of age which followed the development of a nodule in the thyroid gland. The nodule was removed surgically, after which the basal metabolic rate returned rapidly to normal and a small amount of fuzz appeared on the occiput only to fall out four months later. Then she was given cortisone, 50 mg. a day, and after two months of therapy the hair is growing. She still has a patch of baldness on the head which resembles the male type of alopecia.

Dr. Joseph V. Klauder: We all know how difficult it is to draw conclusions. Our basis of therapy was rationalized by the administration of all the components required in the growth of hair; all sulfur-containing amino acids, which are very active ingredients in the growth of all keratin tissue and are required in growth of hair. For example, if sulfur-containing amino acids are omitted from the diet of rats, hair loss results. This, however, does not occur in human beings. Dr. Brown and I discussed this among other phases of sulfur metabolism. It was his idea to give hydrolyzed wool internally. He obtained this by digesting wool by means of hydrochloric acid. The cystine content of hydrolyzed wool is 1.5 gm. per 32 cc. It is a cheap way of giving cystine. We have used it when we wanted to give cystine in treatment of some diseases of the skin. After a lapse of some years, I am still using it. I use it also in cases of dystrophy of the nails and of generalized alopecia, but not with uniform success. I have obtained results similar to those shown this evening in other patients. This woman's hair grew soon after the institution of this therapy and it continued to grow. It is a harmless method of treatment. Of course, in her case we also used estrogenic cream locally. I do not know how much of the result is to be attributed to the estrogenic cream; I have never treated a patient with estrogenic cream only. Our purpose, as practitioners, is to get the patients well; this one got well; she is happy about it; the result is apparently sustained for more than a year now; there is no evidence of loss of hair, and Dr. Gross and I thought it a system of treatment worth calling to your attention.

Dr. Ira L. Schamberg: I was fascinated by the growth of hair in the patient treated with cortisone, inasmuch as the histologic section had shown complete absence of hair follicles. Drs. Peter Flesch and S. B. Goldstone (Depilatory Action of the Intermediary Polymers of

Chloroprene, Science **113**:126, 1951) have recently demonstrated that polymers of chloroprene when applied locally in experimental animals cause temporary loss of hair follicles as well as hair, followed by regeneration of both. The picture induced here by cortisone appears similar.

DR. CARROLL F. BURGOON: My patient had a tremendous amount of greasy yellowish scale spread diffusely over her scalp, in spite of the fact that she had no hair. It is true, as Dr. Schamberg has pointed out, that histologically the site from which we took the biopsy specimen showed nothing like normal hair follicles. In spite of that, in the area in which we did the biopsy, the hair regrew. We have had a patient who lost his hair during corticotropin therapy.

DR. J. M. SCHILDKRAUT, Trenton, N. J.: At the last meeting of the American Academy of Dermatology, Dr. Stephen Rothman mentioned to me that he was obtaining good results in cases of alopecia by giving cortisone, 100 mg. daily for one month. He saw no deleterious effects. His results were not good if the alopecia began before puberty. I have been interested in a young woman who had a total alopecia of the scalp 12 years ago, with a partial regrowth and a complete loss of hair 6 years ago. I prescribed 100 mg. of cortisone a day, and the result has been gratifying. I also have a boy 12 years of age with total alopecia of the scalp to whom I gave cortisone, and in two weeks he showed fuzz over the entire scalp. Although the case is of long standing and prepubertal, the results so far are encouraging.

DR. E. R. GROSS, Wilmington, Del.: There is one other point that should be mentioned —the medicolegal problem. Theoretically, essential amino acids should stimulate cancer cells. If cancer is present in a patient and such a large dose of cystine is given, would it not stimulate the growth of the cancer cells and produce a medicolegal problem?

DR. JOSEPH V. KLAUDER: Brown and others determined the total sulfur content of mouse carcinoma and compared it with such content of other normal growing tissue. It was observed that the rate of growth of the tumors was correlated with the sulfur content; the slower the growth, the less the sulfur content; the more rapid the growth, the greater the sulfur content. This is consistent with the well-known fact that sulfhydryl-containing substances are the essential and universal stimulus for normal growth in plants and animals. We also studied the total sulfur content of carcinoma in the adrenals of mice on a normal diet and on a cystine-poor diet. I do not think there is a medicolegal aspect, as Dr. Gross mentioned. Cancer cannot be cured by diet, nor has it been shown that diet in relation to sulfur-containing amino acids or administration of these compounds accelerates the growth of cancer.

Hemangioendothelioma or Hemangiopericytoma. Presented by DR. IRA LEO SCHAMBERG and (by invitation) DR. DONALD C. GEIST and DR. T. LOFTUS.

K. H., a white woman aged 66, well developed and well nourished, presents in the center of the forehead a raised, boggy, round, red mass. On diascopic pressure fine telangiectatic vessels are seen in this mass. There is edema extending from the mass to the glabella. The lesion is said to have started about one year ago and to have regressed, but not completely disappeared, on treatment with Rhutarb, a remedy for hypertension. Within the last few months the lesion has again begun to grow.

A roentgenogram of the skull showed no abnormality.

Listed below are reports on biopsy specimens.

Dr. Arthur Purdy Stout, professor of surgical pathology, Columbia-Presbyterian Medical Center, New York: "In many of the vessels the endothelial cells were bizarre and had proliferated inside the capillaries. Elsewhere I think it is impossible to say with a hematoxylin and eosin section whether it is endothelial cells or pericytes which have proliferated. Hemangioendothelioma is the most probable diagnosis."

Dr. Frederick Zillessen, pathologist, Jeanes Hospital: "Hemangioendothelioma."

Dr. David Meranze, pathologist, Mount Sinai Hospital: "Hemangiosarcoma or hemangioendothelioma."

Dr. Fred D. Weidman: "I could not see any adequate proliferative process which would qualify as neoplasm, not even a benign angioma. In fact, capillary endothelium was always normal. The few large cells, sometimes multinucleated, were not significantly perivascular. Moreover, they were too scarce to be pericytes. They lay within hemorrhagic spaces. I

regard them as exfoliated endothelium. So far as this section is concerned, the predominant changes were hemorrhagic. It is a local congenital abnormality of capillaries, analogous, perhaps, to cirsoid aneurysm."

Dr. Herman Beerman: "Vascular lesion; rule out hemangioendothelioma."

DISCUSSION

Dr. Herman Beerman: I think this case should not be passed over lightly. When I saw the section, I said that the lesion was vascular tumor, and that hemangioendothelioma should be ruled out.

Dr. Ira L. Schamberg: We certainly are at the mercy of the pathologists, and when they disagree we are on the spot. If this lesion is cancerous, which it appears to be, radiotherapy rather than surgery seems to be indicated.

Granuloma Annulare Following Papular Urticaria or Simulating Papular Urticaria? Presented by Dr. Carroll F. Burgoon Jr.

Tinea Capitis with Unusual Involvement of Hairs of Left Eyebrow and Lanugo Hairs over the Glabella. Presented by Dr. Reuben B. Schwartz.

Lichen Scrofulosorum? Presented by Captain W. N. New (MC), U.S.N. and Commander Bernard G. Greiting (MC), U.S.N.

Case for Diagnosis: 1. Albinism, with Nystagmus, Myopia and Astigmatism, Irregular Teeth, and Supernumerary Toe at Birth: 2. Folliculitis Traumatica of Greenbaum. Presented by Dr. Louis Jaffe and (by invitation) Dr. J. Ross Schmidt, Pottstown, Pa.

Ichthyosis. Presented by Dr. Louis Jaffe.

Bullous Lichen Planus? Presented by Dr. Carroll F. Burgoon Jr.

Granuloma Annulare. Presented by Captain W. N. New (MC), U.S.N., and (by invitation) Lieutenant (jg) J. J. Downey (MC), U.S.N.

Bullous Erythema Multiforme? Pemphigus Vulgaris? Hailey and Hailey Disease? Dermatitis Herpetiformis Factitia? Presented by Captain W. N. New (MC), U.S.N. and Commander Bernard G. Greiting (MC), U.S.N.

Localized Scleroderma. Presented by Dr. Carroll F. Burgoon Jr.

Elephantiasis Nostras? Presented by Captain W. N. New (MC), U.S.N. and (by invitation) Lieutenant (jg) J. J. Downey (MC), U.S.N.

Pemphigus Vulgaris. Presented by Dr. Herman Kline, Atlantic City, N. J.

Pemphigus Vulgaris. Presented by Dr. Herman Kline, Atlantic City, N. J. and (by invitation) Dr. Coleman Jacobson.

Acute Disseminate Lupus Erythematosus with Hypersplenism (Thrombocytopenic Purpura) as the First Sign. Presented by Dr. H. E. Twining and Dr. Carroll F. Burgoon Jr.

Lupus Vulgaris, with Relapse Following Four Years of Vitamin D_2 Treatment. Presented by Dr. Carroll F. Burgoon Jr.

Mycosis Fungoides with Response to Potassium Arsenite (Fowler's) Solution. Presented by Dr. Carroll F. Burgoon Jr.

Sarcoidosis. Presented by Dr. Carroll F. Burgoon Jr.

H. E. Twining, M.D., *Chairman*

Bertram Shaffer, M.D., *Secretary*

May 16, 1952

Parkes Weber Disease. Presented by Dr. Donald M. Pillsbury and (by invitation) Dr. D. Madden.

A. C., a white woman aged 50, presented a large port-wine stain on the inner aspect of the right thigh and leg. The right thigh is 4 in. (10 cm.) larger, the right calf is 1½ in. (3.8 cm.) larger, and the right lower extremity is 1 in. (2.5 cm.) longer than the left. The port-wine stain has been present since birth. About two years ago large varicosities developed on the right lower extremity for which a venous ligation was performed. After this she noted increased size of the right thigh and leg, and recently thrombophlebitis appeared.

The patient has a systolic apical cardiac murmur and late latent syphilis.

The serologic tests for syphilis were positive.

DISCUSSION

Dr. D. Madden (by invitation): Parkes Weber disease includes those lesions, usually occurring on the extremities, combining hemangioma or lymphangioma with increased girth of the extremities. If the angioma occurs from birth, lengthening of the extremity usually is found.

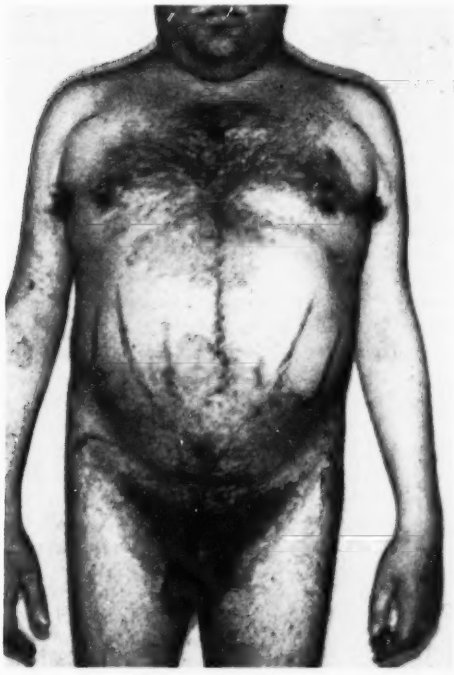

Fig. 1.—Front view of patient with Cushing's striae and complicating T. rubrum infection.

Fig. 2.—Side view. Diffuse phases of the dermatitis low down represent the fungous infection.

Cushing's Syndrome Complicated by Generalized Trichophyton Rubrum Infection. Presented by Dr. Donald M. Pillsbury and (by invitation) Dr. Coleman Jacobson.

S. M., a white youth aged 19, of short stature, with moon facies and florid complexion, presented about the neck, on the sides and the upper part of the chest, in the groins, and on the right arm a circinate, scaling, reddish-brown eruption with no central clearing of the patches. The right palm is diffusely erythematous and scaling. All the nails of this hand are elevated and show hyperkeratosis and longitudinal ridges. The feet and legs are involved in a stocking-like fashion. There are many purple striae on the thighs, buttocks, and arms.

Four years ago the striae appeared on the buttocks, arms, and thighs, associated with a florid moon face, short stature, and hypertension. The circinate scaling lesions developed two years ago.

The blood pressure was 180/50; blood studies revealed 11 gm. of hemoglobin per 100 cc. 3,400,000 erythrocytes, and 7,800 leucocytes, with 84 per cent neutrophiles, 3% monocytes and 5% lymphocytes. The blood urea nitrogen was 13 mg. and the fasting blood sugar 76 mg. per 100 cc. Results of urinalysis were within normal limits. Examination of potassium hydroxide preparations and a McManus test were positive for fungi.

DISCUSSION

Dr. Albert M. Kligman: The crucial factor in successful management of a Trichophyton infection seems to be individual susceptibility. All patients seem to respond well at first to various remedies, but relapse is almost invariable.

Dr. Fred D. Weidman: The Cushing striae are remarkable. I doubt that anybody in this audience has seen so extreme and bizarre an expression. The bizarreness and the symmetrical character of these striae are intriguing, but the patterning is not that of the metameres. The striae are annular, circular, and transverse on the legs below the knees, whereas they extend longitudinally on the other parts of the body. In other words, there is no systematization in the patterning. Is there any specific evidence of pituitary disease in this patient? I did not see any low hair line or other external evidence of hypopituitarism.

Dr. Frederick Urbach (by invitation): This patient was studied very carefully by the department of endocrinology, and I believe that there is some x-ray evidence of disturbance of the sella turcica. All the findings point to his having a pituitary rather than an adrenal lesion.

Dr. John F. Wilson: About a year ago we saw this patient at Jefferson Hospital. At that time the striae were much darker than they are now and presented an even more bizarre picture. According to his history, these were the first changes that occurred on his skin. The T. rubrum infection was much worse than it is now. His first response to treatment with simple therapeutic measures was dramatic, but relapse occurred soon after he rejected further hospitalization.

Mycosis Fungoides: Recrudescence After Treatment with Nitrogen Mustard. Presented by Dr. Donald M. Pillsbury and (by invitation) Dr. Frederick Urbach.

J. S., a white man aged 74, fairly well developed and with no evidence of systemic involvement, has had a generalized desquamative erythematous eruption of eight years' duration.

In 1951 many large infiltrated plaques developed on his chest, arms and thighs, with marked pruritus. He was treated with triethylene melamine from June, 1951, to December, 1951, with moderate improvement of the pruritus and erythema but no effect on the tumor masses. Between courses he received 3 gm. of cortisone, which apparently caused the marked aggravation of the cutaneous lesions. In January, 1952, the patient received a total of 45 mg. of nitrogen mustard (HN2H methyl-*bis* [β-chlorothyl]-amine), intravenously, three weeks after discharge. The cutaneous lesions cleared remarkably and finally disappeared, leaving only diffuse erythema. In the past six weeks new infiltrative lesions have appeared and seem to be extending.

At present the skin, in general, is dry and large areas of the thighs, trunk, and chest are diffusely reddened. On the face and over the thighs, buttocks, and legs there are irregular plaques of infiltration bordering on tumor stage, which are exudative or are covered with a thick whitish scale.

Blood studies revealed 60% hemoglobin, 3,400,000 erythrocyte, and 5,700 leucocytes. Urinalyses gave values within normal limits. A roentgenogram of the chest showed no abnormalities.

Dr. Herman Beerman reported the biopsy specimen as showing mycosis fungoides.

DISCUSSION

DR. LAWRENCE KATZENSTEIN, Wilmington, Del.: I should like to report another patient with mycosis fungoides who was given a so-called full course of nitrogen mustard, with great improvement. After three months he has no new lesions.

DR. FREDERICK URBACH (by invitation): We have now treated five patients with mycosis fungoides with nitrogen mustard intravenously. In two patients to whom we gave the full dose, 0.1 mg. per kilogram of weight × 4, we had unfortunate results. Involution of all lesions was followed by ulceration and eventually death. Since then we have treated other patients with excellent results, and we attribute the difference to the fact that we give no more than 6 mg. once every day or once every other day, with rest intervals. The other interesting point is that we have noted in patients with a good response that the involution did not occur immediately, as it does in lymphomas, but that there was a lag of two or three weeks, after which the improvement was rather spectacular. In Hodgkin's disease improvement is very rapid, a matter of days.

Blastomycosis Cutis. Presented by DR. T. KEMP (by invitation) and DR. BERTRAM SHAFFER.

W. S., a Negro man aged 45, presents an extensive granulomatous and scarring process of the central facial area, involving the upper lip, the nose, both cheeks, and the left lower eyelid. The process is chiefly atrophic and scarring, with contraction of the nose and shrinkage of the nares, with large islands of depigmentation in the center. The upper portion of the lesion is an active elevated band of verrucous papillary abscesses.

Eight years ago this man noticed a small papular growth on the left upper lip, which continued to spread while he was under treatment for lupus vulgaris.

The general medical examinations gave results which were not remarkable. The blood cell counts and results of urinalyses were within normal limits. The serologic tests for syphilis were negative. X-rays of the chest were normal. A prostatic smear was normal. Culture of pus from the lesion for fungi has produced only contamination bacteria as yet.

The biopsy specimen was reported as blastomycosis with Blastomycetes demonstrated. A review of slides made in 1946 showed the same histologic picture as the 1952 slide, and Blastomycetes could also be demonstrated.

DISCUSSION

DR. CARROLL S. WRIGHT: Dr. Arthur C. Curtis reported four cases at the recent meeting of the American Dermatological Association with cutaneous and lung lesions of blastomycosis completely cured after treatment with stilbamidine. He regarded the result as not due to hormonal action but as a specific effect.

DR. HERMAN BEERMAN: The most instructive feature of this case is that some eight or nine years ago a biopsy specimen was removed but was not diagnosed as blastomycosis. Recently I saw a second specimen and, although the tissue reaction was perfect, I could not find the organisms. I reviewed the older specimen and again made this diagnosis, but again I could find no organisms. Further study of the slides at great length eventually revealed a few organisms even with hematoxylin and eosin stains, and the McManus stain verified it. Here is a particularly important case that calls attention to the fact that blastomycosis must be suspected in a section which shows the histologic features that this man's lesions did. The patient would have had a great deal less scarring had the original specimen been properly diagnosed. One must keep the deep mycoses in mind, even though one cannot find the organism. I think the McManus stain should be used in more cases of this type.

DR. ALBERT M. KLIGMAN: I think we must reserve our opinion that stilbamidine is a specific cure for blastomycosis. Many think that the disease responds to iodide, whereas others completely reject this notion. The fact is that blastomycosis has a tendency toward spontaneous healing, as do many other diseases, which makes therapeutic evaluation difficult.

Miliaria Profunda. Presented by DR. W. B. SHELLEY and (by invitation) DR. H. J. HURLEY.

G. W., a white man aged 25, states that he has been unable to sweat, following an attack of pertussis at the age of 3 months. Whenever he is exposed to heat or upon exercise, numerous

noninflammatory, nonpruritic papules develop. The skin becomes edematous, and the patient is unable to close his fist. He is very intolerant to heat, manifesting weakness, hyperpnea, and hyperthermia. Upon cooling, the papules undergo almost complete involution. The residual papules are regularly spaced and give the skin a morocco-grained appearance. They are not associated with hair follicles and number 50 or 60 per square centimeter.

The report on the biopsy specimen stated that the skin was normal except for the presence of a localized dilatation of a sweat duct in the dermis.

In 1949, the patient was treated with vitamin A, orally and by injection, with remarkable objective improvement. However, this treatment was discontinued because of gastrointestinal symptoms. Incidentally, the local introduction of atropine prevents the appearance of papules during heating.

Juvenile Xanthoma. Presented by DR. JOHN F. WILSON.

D. E. L., a white boy aged 17 months, presents a small bright-yellow nodule, about 3 mm. in diameter, below and behind the left ear. There is a similar but smaller lesion on each cheek. The child has had infantile eczema of the cheeks, which is now improved. His grandfather died of diabetes.

There is no evidence of involvement of any other organs.

The blood cholesterol was 314 mg. per 100 cc. of blood. The urine was negative for sugar.

DISCUSSION

DR. CARROLL S. WRIGHT: I have seen at least three of these cases in the last six or seven years. All have been easily cured by shelling out with the skin curet after injection of a drop of procaine. The base is touched with trichloroacetic acid, and no scar is left.

DR. LAWRENCE KATZENSTEIN, Wilmington, Del.: Is this nevoxanthoendothelioma?

DR. FRED D. WEIDMAN: In juvenile xanthoma the lesions are generally more numerous; it is a more widely disseminated disease. I do not believe that there is anything about the individual lesion which is distinctive except that the nevoxanthoendothelioma would probably be a little more congested. Of course, histologically there is a very definite difference. In nevoxanthoendothelioma there is a very large factor of capillary hyperplasia and there are some large nevus-like cells. It is these capillaries which are responsible for the reddish cast of the lesion clinically.

DR. FREDERICK URBACH (by invitation): One feature of this case is that the cholesterol value was 314 mg. per 100 cc. obtained by the Sperry method and, therefore, would be considered definitely normal. It seems to me, after a review of the literature, that there is a confusion in terminology in connection with juvenile xanthoma by different authors. Of course, the only importance of this lies in making sure that this boy does not have xanthoma tuberosum of the infant. We have a child under our care with xanthoma tuberosum in whom the first lesions began at the age of 17 months. Such patients are destined to early death from cardiac complications. It is therefore important clinically to know whether this child has juvenile xanthoma, which is not associated with arteriosclerosis.

CORRECTION

In the Directory of Dermatologic Societies published in the February issue, errors were made in listing the officers of the Los Angeles Dermatological Society and the Metropolitan Dermatological Society of Los Angeles. Walter Schwartz, 696 E. Colorado Blvd., Pasadena, Calif., and J. Walter Wilson, 3875 Wilshire Blvd., Los Angeles, are the president and secretary respectively of the Los Angeles Dermatological Society. Stanton B. May, 119 N. Central Ave., Glendale, Calif., and Irving A. Lewe, 3319 W. Beverly Blvd., Montebello, Calif., are president and secretary respectively of the Metropolitan Dermatological Society of Los Angeles.

The officers of the Chicago Dermatological Society were incorrectly listed in the February issue. They are Samuel J. Zakon, 185 N. Wabash Ave., President; William K. Ford, Rockford, Ill., Vice-President, and Irene Neuhauser, 7 W. Madison St., Secretary.

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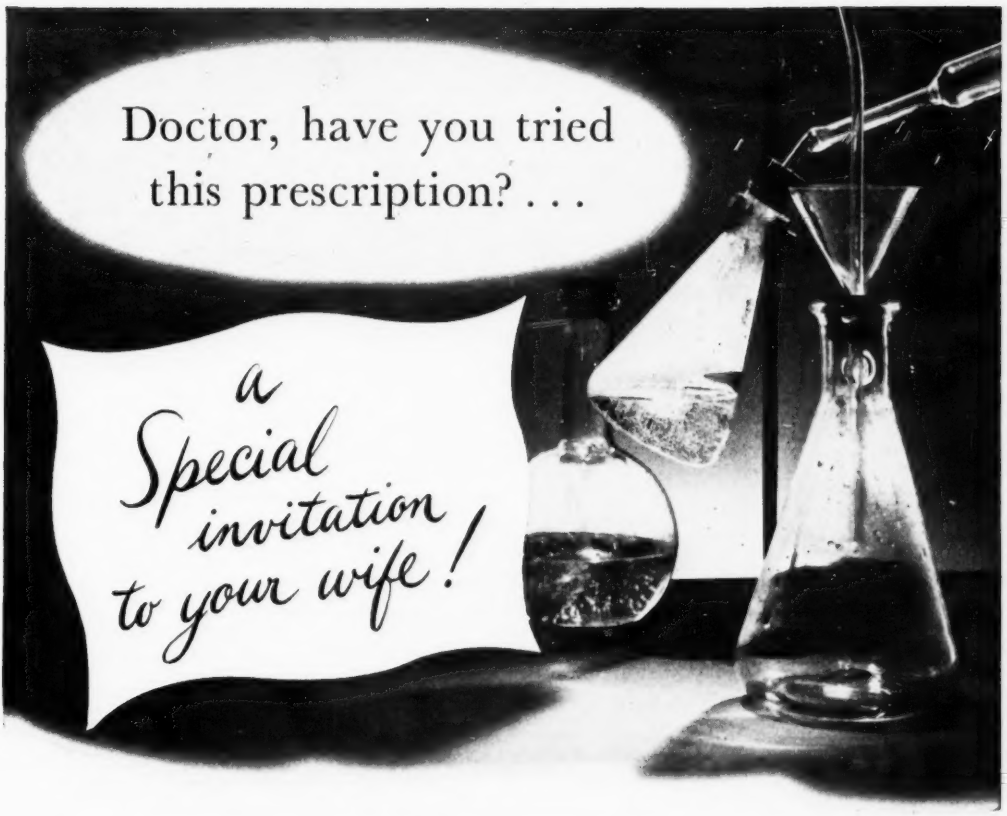

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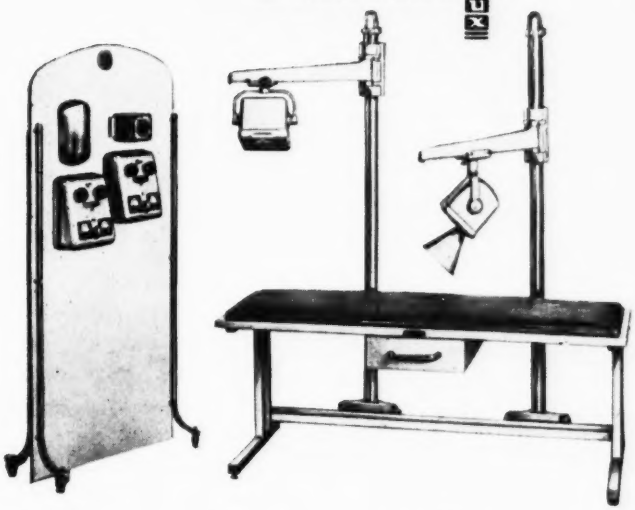

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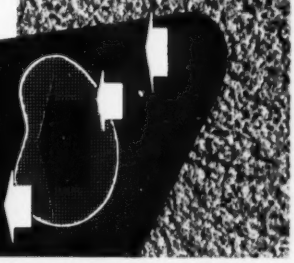

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References:

1. Rothman, J. and Shapiro, A. L.: Med. Clin. N. Amer. 33:274-5, Jan., 1949.
2. Stieglitz, E. J.: Geriatric Medicine, p. 848, 1943.

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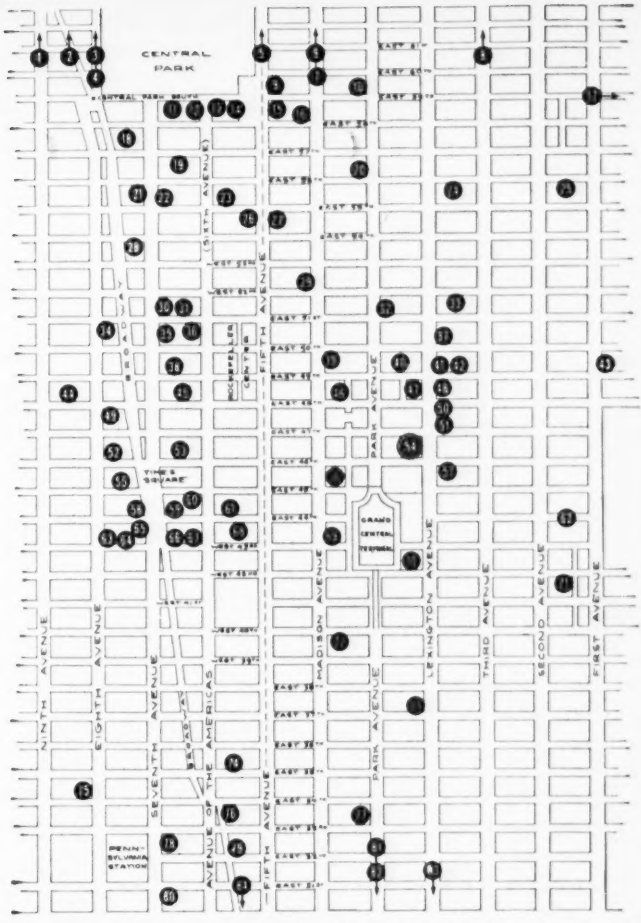
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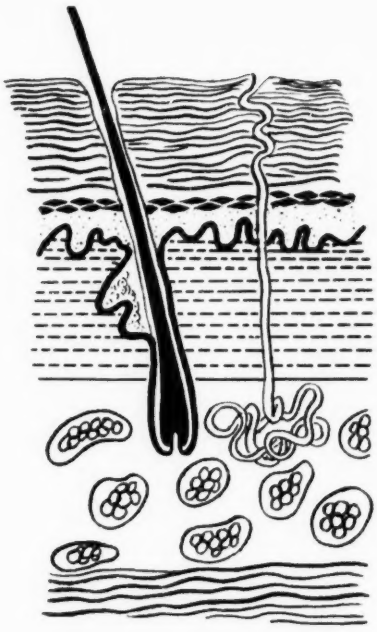

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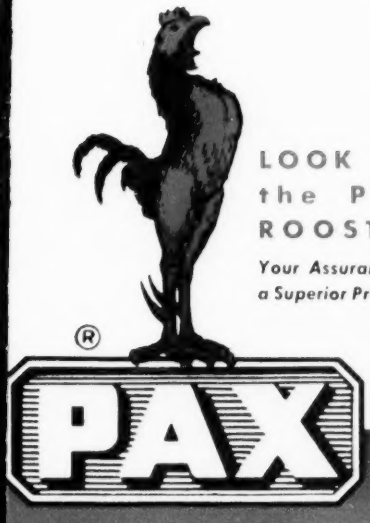

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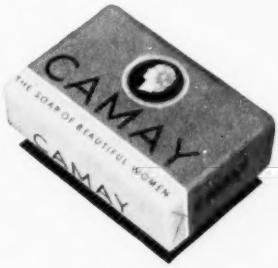

Camay

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